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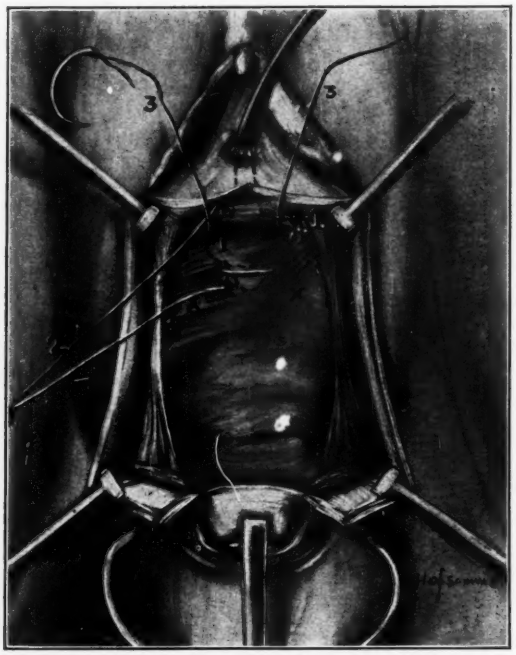

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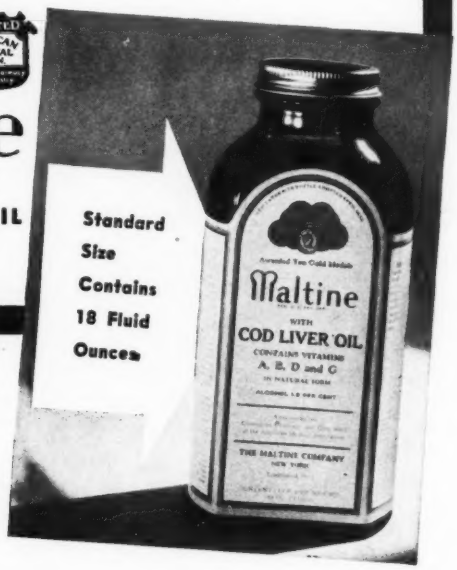

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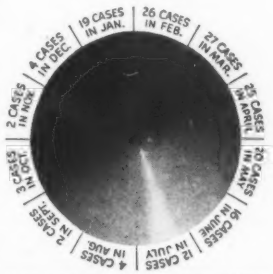
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* "Six Years Clinical Experience with Viosterol," Shelling and Hopper, Page 165, Bulletin of Johns Hopkins Hospital, Vol. LVIII, No. 3, March 1936.
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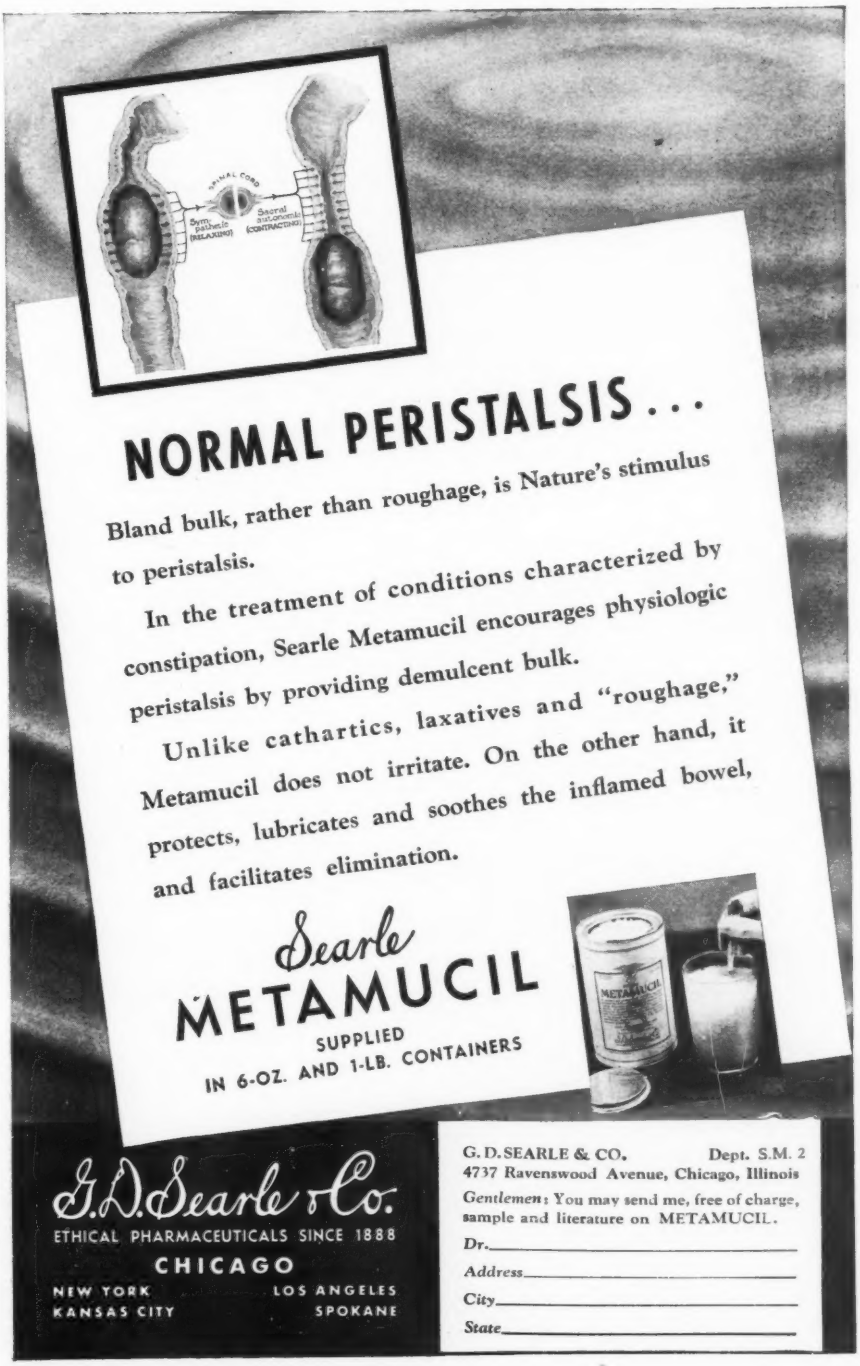

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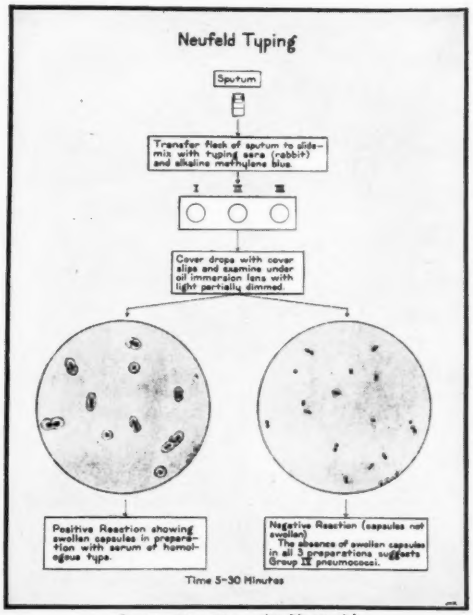
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THE DEVELOPMENT OF THERAPEUTIC RABBIT SERA for the higher type pneumococcus pneumonias is important news. Now physicians are afforded a specific measure for the treatment of pneumonia types some of which (notably Type 3) frequently terminate fatally and for which routine therapeutic measures only have heretofore been available. Clinical results with some of these serum types have been highly encouraging as far as they have gone and there have even been cures of bacteremic cases in Type 3 and other higher-numbered type infections.

Lederle Laboratories now announce rabbit sera for Type 3, Type 6 and Type 14. Sera for additional types will follow within a few weeks in the expectation that therapeutic sera for all 32 types of pneumococcic pneumonias will become available during the winter.

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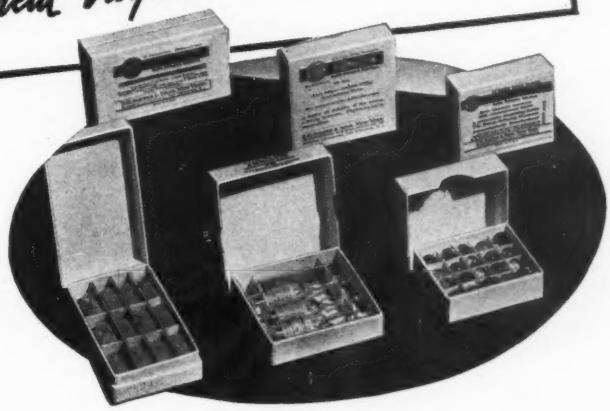

CONCERNING the management of gonorrheal vaginitis, Lewis[1] states: "We consider the use of vaginal estrogenic suppositories the most effective method known for the treatment of gonorrheal vaginitis in children."

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For literature address Professional Service Department, 745 Fifth Avenue, New York

[1] Lewis and Adler: *J. A. M. A.* 106:2054, 1936.
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(Grams per 100 c.c.)	Cow's Milk	Breast Milk	Similac
Calcium combined with Protein	.054 gm.	.024 gm.	.030 gm.
Mono-Magnesium Phosphates	.103 gm.	.027 gm.	.027 gm.
Di-Calcium Phosphates	.175 gm.	.000 gm.	.000 gm.
Di-Potassium Phosphates	.230 gm.	.000 gm.	.000 gm.
Potassium Citrates	.052 gm.	.103 gm.	.103 gm.
Sodium Citrates	.222 gm.	.055 gm.	.055 gm.
Calcium Citrates	.119 gm.	.059 gm.	.059 gm.
Iron	Trace	Trace	Trace
Sulphur with Protein	.022 gm.	.001 gm.	.001 gm.
Phosphorus with Protein	.022 gm.	.001 gm.	.001 gm.

C. W. Martin, M. D., New York State Journal of Medicine. September 1, 1932.

A SALT BALANCE OBTAINED ONLY BY LABORATORY METHODS

Fat 2%, proteins 1.6%, and sugar to make up the lack of calories that results from dilution — that, roughly, is the home method of "modifying" cow's milk for the baby. ¶ And what of the minerals? Are they not equally as important as the other food substances? ¶ The laboratory method of rearranging cow's milk, by which Similac is prepared, not only adjusts the percentages of fats, proteins and carbohydrates, but alters the salts of cow's milk in character and in relation to each other. Similac has a salt balance that cannot be obtained in the ordinary milk dilution or modification—one of the reasons for the excellent result obtained with this laboratory modification.

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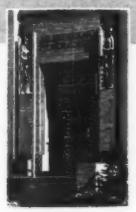

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Fat	**1.8 grams** (entire period)
Carbohydrates	**6.0 grams** (early infancy) **4.7 grams** (later months)
Minerals	**0.5 grams** (entire period)
Fluid Volume	**3 ounces** (first month) **2½ ounces** (2nd and 3rd months) **2 ounces** (later months)

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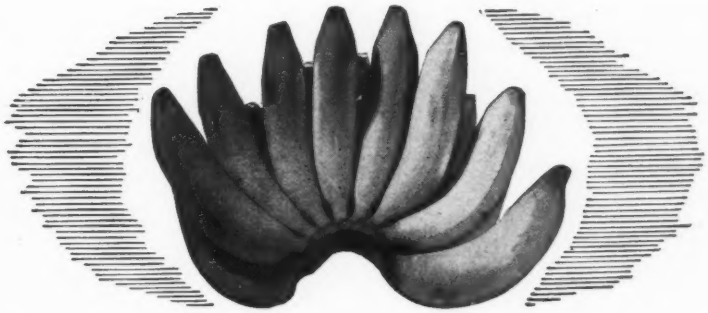

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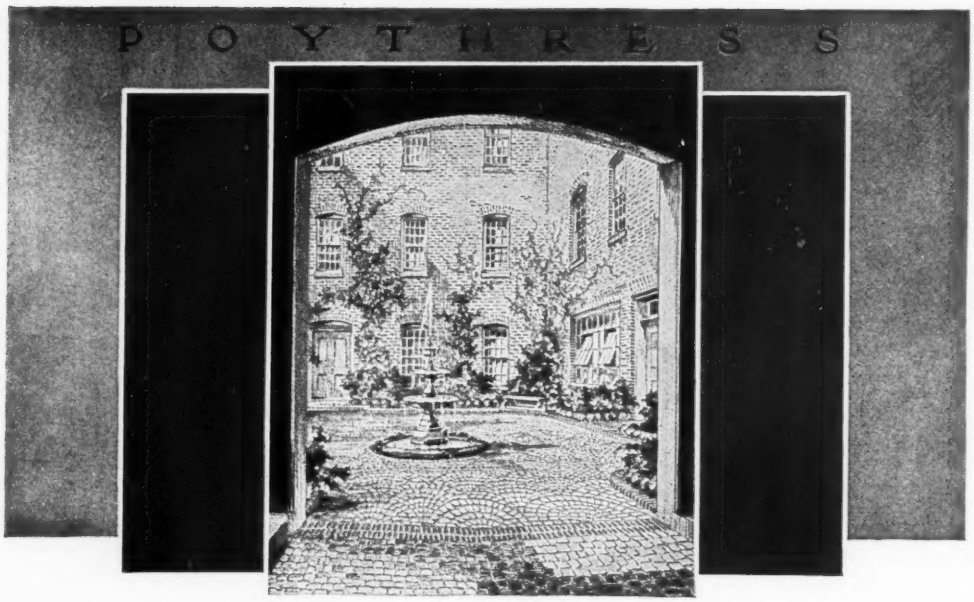

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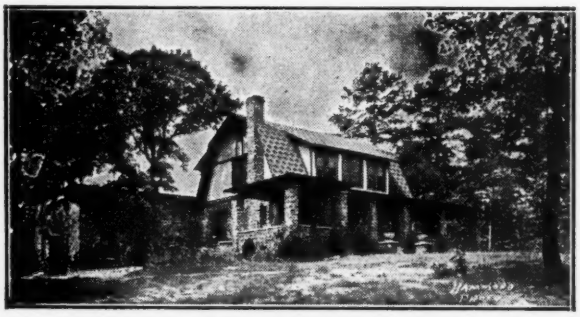

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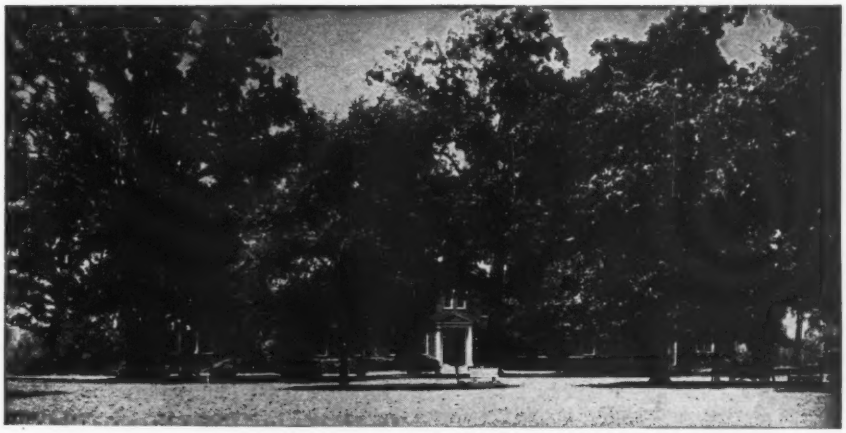

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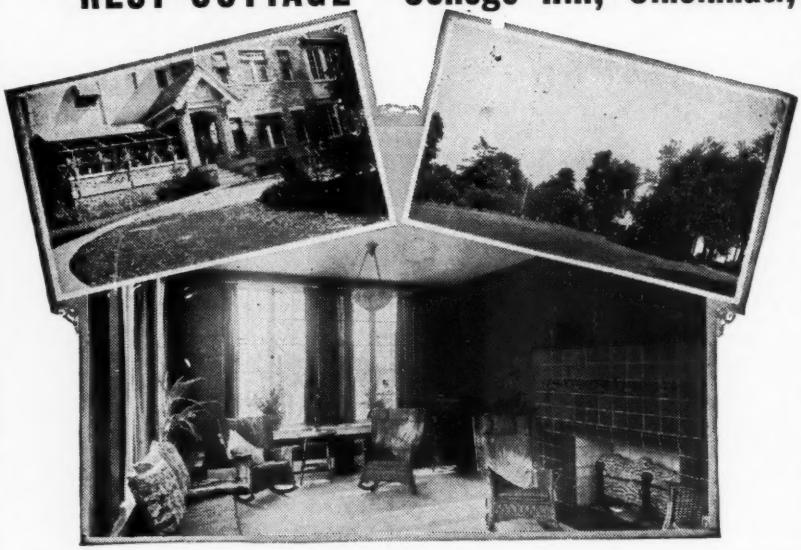

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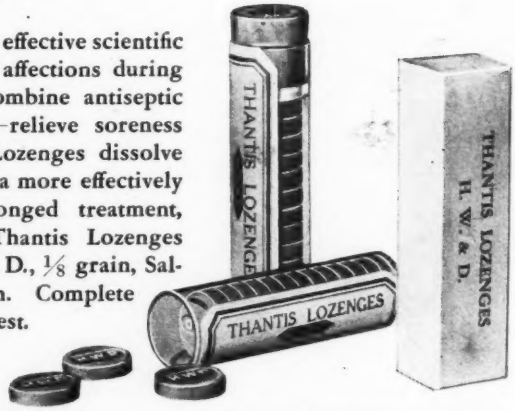

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ANGIOID STREAKS OF THE CHOROID AND PSEUDOXANTHOMA ELASTICUM*

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and
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Angioid streaks of the choroid and their apparent association with pseudoxanthoma elasticum have received much attention in the literature since the first reports by Groenblad in 1929, by Marchesni and Wirz in 1931, and by Clay in 1932, all of which were independent observations.

Since 1932, twenty-eight cases of angioid streaks associated with pseudoxanthoma elasticum have been reported. Although few cases of either disease have appeared without the other, notable reports of such conditions have been made by Benedict and Montgomery and by Finuerud and Nomland. No reported cases have been associated with senile elastosis with the exception of those reported by Biozzi and by Clay.

Angioid streaks have been found to occur without pseudoxanthoma elasticum, and in the same way, pseudoxanthoma elasticum has occurred without angioid streaks. However, the association has been found to be the rule, and there must, therefore, be some common pathogenic factor.

In 1925, we saw two cases of angioid streaks, one of which was associated with pseudoxanthoma elasticum. However, since there had been no previously reported association of the streaks with pseudoxanthoma elasticum, we did not report our findings. Then, in 1930, we found two more cases in which the conditions were associated. Since 1930 we have seen fourteen other such cases, making a total of eighteen. All of these have been observed in private practice, except one Negro patient, who was seen at the out-patient eye clinic of Emory University. It would seem, therefore, that angioid streaks are more common than a review of the literature would indicate. In 11 of the 18 cases, there was pseudoxanthoma elasticum, in 2 senile elastosis, and in 5 no skin involvement at all. However, in the cases without pseudoxanthoma elasticum there were very few streaks, and in the cases with the most marked streaks invariably there has been more skin involvement.

The microscopic pathology of angioid streaks is still unknown, since no authentic case, except that of Benedict, has been reported, and, unfortunately, in that case after fixation streaks were not visible. Unless someone is able to examine a case in the very early stages of disease, we doubt that pathologic studies will throw much light on the question, since marked secondary alterations such as inflammatory and atrophic changes materially alter the true pathologic picture.

In a personal communication concerning a slide of supposed angioid streaks seen in Vienna, Austria, Dr. A. B. Reese states: "I can say though that this is a most unusual finding in an eye, but whether or not it represents the actual pathology of this condition, I cannot say. There is a dehiscence in a thickened lamina vitrea over which there is a fibrous fusiform-shaped lesion which is between the lamina vitrea and the pigment elipthelium. In this fibrous plaque there is a blood vessel."

Since 1932, the only notable explanation for the streaks has been given by Wassenaar, who, however, has advanced a rather fanciful and impracticable theory as to their development. He states that angioid streaks are caused by an anomaly of development resulting in an ectopia

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*From Emory University School of Medicine.

of blood vessels. These abnormal vessels are placed between the two blades (the pigment epithelium and the retina proper) of the secondary eyecup, where they anastomose, branch and spread. These vessels are especially vulnerable, reacting to any infectious material carried through them and thus developing periarteritis and periphlebitis, and these changes give the picture of streaks.

Terry presents an interesting observation and attempts to link osteitis deformans with angioid streaks because in three of his five cases osteitis deformans was also present. Since osteitis deformans is a relatively common disease, a comparative study might apply to any rare retinal disease. No case in our series of 18 presented any symptoms of osteitis deformans. In five cases with angioid streaks and pseudoxanthoma elasticum, our studies included x-rays of the bones of the skull, long bones, serum calcium, phosphorus and serum phosphates. All were normal. Terry's description of the fundus picture is so incomplete that one wonders if some of his cases were genuine. Might not some other disease of the fundus oculi be common to osteitis deformans? Certainly what he classifies as the typical "halo" has not been the characteristic picture in our 18 cases.

The fundus picture has been described so often that we will not repeat it, but will point out certain observations we have made in our 18 cases.

In one case we watched the streaks develop. At the first examination the fundus was normal except for several small choroidal hemorrhages. Two weeks later the hemorrhages were slightly increased and in the areas of the hemorrhages there appeared reddish streaks radiating out from the nervehead in the characteristic manner. Four weeks later all the hemorrhages had disappeared and the streaks had become reddish-brown. After a year, no new streaks had appeared and along most of the old ones atrophy of the choroid was developing. Our observation has been that hemorrhages may occur early, but are not common later in the disease. The most common type of hemorrhage is the smaller choroidal hemorrhage always seen in the neighborhood of the streak. If the hemorrhage is large and not situated in the macula, it will be diffused with rather even edges definitely under the retina, as will be shown in one unusual case we are reporting. Hemorrhages are not uncommon in the macula provided a streak runs in that direction; here the hemorrhage most frequently extends into the retina and usually after the absorption of the hemorrhage there are marked atrophic changes. There is also an increase of fibrous tissue, giving the appearance of diskiform degeneration of the macula, and this same picture may occur elsewhere in the retina if the hemorrhage has extended further. The streaks are always bilateral and almost uniform in their involvement of the two eyes. There may be only one streak in a fundus, but usually there are many, and if there be only one or two streaks they start from the disc border and extend outward, though rarely past the equator. When the circular streak occurs it is never complete and is usually near the disc border, more conspicuous on one side of the disc. From this point radiating streaks are seen, and it is not unusual to see the streaks anastomose. The streaks are usually small with serrated borders and resemble blood vessels in their course. However, the streaks may be straight and extend beyond the limit of vision, as in one case we are reporting. In the beginning the streaks are reddish, later reddish-brown. After several years these almost disappear, and are replaced by marked choroidal atrophy. No streaks show any black pigmentation except in rare, small areas where there have been no hemorrhages. In our Negro case a great deal of pigment was seen along the streaks; this might be expected in view of the large amount of pigment characteristic of this race. The streaks usually lie just beneath the retina and in the choroid, but in one case in which some of the streaks extended beyond the equator these streaks appeared to lie much deeper in the choroid.

One new observation which we have made concerning the streaks is that if the streaks are seen early and do not contain much brownish pigment, they can be seen to disappear on pressure upon the ball. This observation, we believe, definitely establishes the fact that the streaks are vessels. Using the Friedenwald ophthalmoscope and the red filter, the streaks are not visible; with the red-free filter the streaks are more prominent. This observation has only been made on the two most recent cases, the same observation being concurred in by three of our colleagues. Dr. F. Phinizy Calhoun reports that on the same day he made this observation in our case he had a similar experience with another case. If, then, the streaks were due to cracks in the lamina, they should increase in size; if they were due to a fibrosis, they should not be altered.

The retina shows no gross lesion except in the few cases in which the macula becomes in-

volved. The retinal blood vessels have been carefully observed and show no involvement except in the older patients in whom senile arteriolar sclerosis was present.

The nervehead is never involved from the disease. In two cases hyaline deposits were seen on the nervehead, but there could be no relationship.

We are reporting the case of a girl, 21 years of age, the youngest so far reported in the American literature. Blobner reports two cases in brothers, 16 and 20 years of age. In most of our cases the age was from 40 to 60.

The family history in most of our cases was essentially negative: in many we were able to examine brothers and sisters. In one instance, however, both angioid streaks and pseudoxanthoma elasticum were noted in a brother and sister. Five brothers and one sister of the last patient reported here were examined with negative findings.

Complete medical examination was done in eleven cases of angioid streaks with pseudoxanthoma. Mild diabetes was present in one case. Other diseases, including hypertension and syphilis, were absent in all 11. A case reported by Clay in 1932 has been seen by us at six-month intervals, and from time to time has had x-rays of bones with negative findings.

A complete report of three unusual cases of angioid streaks and pseudoxanthoma elasticum recently seen will be given. The first case is the only one so far reported in a Negro. The second patient is the youngest reported in this country, and is the only case showing large straight and long streaks extending beyond the equator. The third shows a larger number of anastomoses of streaks than we had previously seen, and demonstrates the location of the hemorrhage as seen from the photograph of the left eye.

REPORT OF CASES

Case 1.—M. W., a colored woman, aged 42, came to the clinic November 8, 1935, complaining only of poor vision for close work. She had never worn glasses. She had never had any serious illness and had always worked hard. The family history was negative throughout, especially in regard to eyes. She was hospitalized and checked carefully with the following results: physical examination showed no organic disease. Wassermann tests of the blood and spinal fluid were negative. Urinalyis showed no sugar or albumin. Blood phosphorus and calcium were within normal limits. Blood sugar was 100 mg. X-ray studies of the pelvis, femur, hands and skull showed no evidence of Paget's disease. The electrocardiogram was normal. Basal metabolism was —6. The Montoux test was negative after 24 hours. Neurologic examination by Dr. Richard B. Wilson was negative. Examination of the skin showed presence of pseudoxanthoma elasticum on each side of the neck.

Vision was 20/20 in each eye. No ptosis was present, the lid margins were clear, the conjunctiva showed no injection. The pupillary reaction was normal to light and accommodation. The lens and media were clear.

In the right eye, the papilla was small and round; scleral and choroidal rings were present; the cup was shallow, lamina cribrosa was not seen. The vessels were normal in size and relationship; around the disc choroidal pigment was increased. At 12:00 o'clock on the disc border a brownish streak extended upward, running into a clump of black pigment. A companion streak extended parallel; both of these extended into

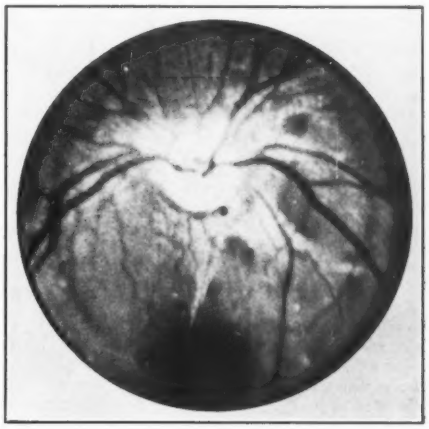


Fig. 1
Angioid streaks of the choroid as seen in Negro. Right eye. Case 1.

Fig. 2
Angioid streaks of the choroid as seen in Negro. Small hemorrhage present. Left Eye. Case 1.

the periphery, becoming more threadlike. A number of less prominent streaks, following a zigzag course resembling blood vessels, extended out from the disc to the periphery. There was definite choroidal thinning along their course and in the periphery some old choroiditis with a few deep retinal hemorrhages. The retina in the periphery showed fine pigmentation.

In the left eye, the atrophic areas around the disc showed rather jagged star points from which radiated the small dark streaks. The largest streak began at 3:00 o'clock and extended towards the macula. These streaks were small and threadlike and did not resemble those seen in the Caucasian race. These streaks did not entirely disappear with pressure and with the red filter showed much greater pigmentation along the edges than those observed in the white race.

The diagnoses were: angioid streaks of the choroid, and pseudoxanthoma elasticum.

Case 2.—Miss L. P., aged 21, consulted us in November, 1936. She had worn glasses irregularly for ten years. For the previous year she had had trouble reading and for two months her vision had failed more rapidly. She had been extremely nervous, especially since graduating from college. Her first teaching assignment had been too much of a strain for her, so she gave it up after two weeks and had been melancholy since that time. On several occasions she had threatened suicide. She was depressed at the time of the examination and it was difficult to get answers from her. Her past history was negative except for moods of depression. She had never had a serious illness. The family history was irrelevant.

Physical examination showed nothing but poor development and undernourishment. Special examinations were as follows: urinalysis showed a trace of albumin and acetone. Blood phosphorus was 3.8 mg. and blood calcium was 9.3 mg. Wassermann and Kahn tests on blood and spinal fluid were negative. Blood sugar test was high, 300 mg. The red cell sedimentation test was negative. X-ray studies of pelvis, femurs, hands and skull by Dr. J. J. Clark showed no evidence of Paget's disease. The electrocardiogram was essentially normal. The basal metabolic rate was —25. The Mantoux test was negative after 24 hours. Dr. Wilson summarized his neurologic examination as follows:

"Evidence suggests a disturbance of the left cerebrum. In one who has taught school the present state indicates a mental deterioration. From her history it seems more like a reactive depression. It is impossible to say whether the left cerebral disturbance is old or a progressive process. It would be advisable to recheck her neurologic status after a few months."

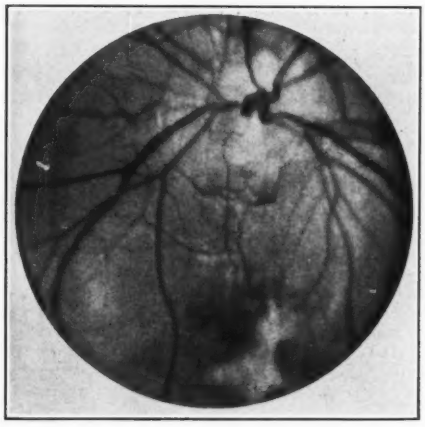
Dermatologic examination showed pseudoxanthoma elasticum over neck and popliteal space.

Vision in her right eye was 20/50, left eye 20/100 with correction. Tension with Schiotz tonometer in each eye was 18. There was no ptosis present; the lid margins were clear; the conjunctivae were not injected. The muscle excursion was good in the cardinal directions of gaze; the cornea was normal with loupe and slit lamp. Pupillary reaction was normal to light and accommodation.

In the right eye, the media were clear; the nerve-head was oval; a moderate cup present and the lamina cribrosa faintly seen. The retinal vessels were normal in caliber and relationship. Around the papilla were irregular reddish-brown streaks, some of which were communicating. From these, streaks radiated out in all directions. These streaks were twice the size of retinal vessels and seemed to be in the first portion of the choroid. The largest one ran out towards the macular region beyond the line of vision with the ophthalmoscope. No hemorrhages were visible in the eye.

In the left eye, the appearance was similar except for a streak going directly to the macula, where there was an organized grayish mass, slightly elevated with pigmented edges. Beyond this extended a streak that disappeared in the periphery. Pressure on the eyeball caused fairly complete disappearance of the streaks along with the retinal vessels. Some pigment along the

Fig. 3
Unusual type angioid streak of the choroid seen in a girl of 21. Right eye. Case 2.



Case 4
Macula involvement in girl of 21, with angioid streak of the choroid. Left eye. Case 2.

large streak did not disappear. The red filter with the ophthalmoscope caused almost complete fading of the streaks except where pigment was present.

The diagnoses were angioid streaks of the choroid; pseudoxanthoma elasticum, and dementia precox.

Case 3.—R. F., a farmer, aged 44, consulted us on October 20, 1937. He had never been troubled with his eyes until three months before, at which time the left eye began to fail suddenly. His history was negative. The family history was irrelevant. Five brothers and one sister examined by us showed no streaks or pseudoxanthoma elasticum, but the sister showed a small central choroidal lesion in the left eye. Physical examination showed a well-developed and nourished man with no related organic disease. Special examinations were as follows. Urinalysis showed a faint trace of albumin present. Examination of feces was negative. Wassermann and Kahn tests on blood and spinal fluid were negative. Constituents of the blood in milligrams per 100 c. c. were as follows: cholesterol 150; phosphorus 2.7; calcium 10; sugar 95; urea nitrogen 21; nonprotein nitrogen 43; creatnine 1.2. X-rays of pelvis, lower spine, femur, tibia and fibula and forearms showed no evidence of Paget's disease. The basal metabolism was plus 7. Dr. Wilson, on account of altered reflexes, thought that there was a left cerebral disturbance. The significance of this is undetermined.

Dermatologic diagnosis was pseudoxanthoma elasticum. Dr. E. L. Bishop reported a biopsy: "Sections show a normal appearing surface epithelium with intact basal layer, under which are normal glands and hair follicles. In the connective tissue are found a number of elastic fibers, with beginning degeneration, and in one place a large mass which has practically completely degenerated appears as clumps of basophilic granular amorphous material without fiber or strands. There is no evidence of any active infection. Lipoid and xanthomatous cells are lacking and there is no pigment. The diagnosis is pseudoxanthoma elasticum; elastic degeneration."

The patient had never worn glasses and his vision uncorrected was 20/15 and 5/200. The tension was 18 Schiotz.

Ocular examination showed the lids not ptosed and the margins clear. The conjunctiva showed no injection. Muscle movements were good in all cardinal positions. The cornea, lens and media were clear.

In the right eye, the nervehead was round; cup absent; lamina cribrosa not seen; arteries and veins were normal in caliber and relationship. Around the papilla numerous irregular reddish-brown lines resembling choroidal vessels radiated out from the disc border. One streak extended to the edge of the macular area and connected with a grayish atrophic lesion surrounded by some pigment. No hemorrhages were present.

In the left eye, the papilla was surrounded by an extensive hemorrhage about one disc diameter in width except where it extended toward the macula. Its temporal border gave the appearance of hanging over the nervehead. From the hemorrhage the numerous streaks extended in all directions, continuing slightly past the equator. Many of these were irregular in their course and communicated with each other. There were several small hemorrhages in the macular area with one streak extending through a hemorrhage. Pressure on the eyeball caused complete disappearance of the streaks as well as of the retinal vessels. The red filter on the Friedenwald ophthalmoscope caused complete fading also.

The diagnoses were angioid streaks of the choroid; and pseudoxanthoma elasticum.

The following is a report by Drs. Jack W. Jones and Herbert S. Alden, who examined these three patients and who made the diagnosis of pseudoxanthoma elasticum:

"Pseudoxanthoma elasticum is a condition of the skin in which there is elastic tissue degeneration in the corium occurring in the areas of the body where stretching and

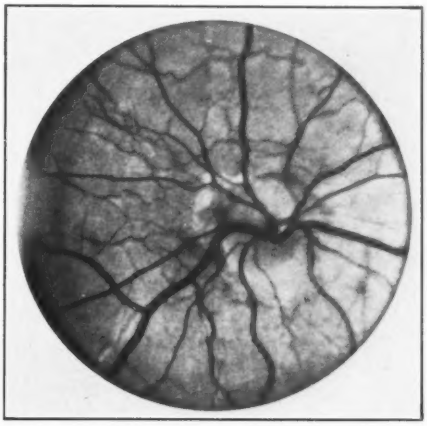


Fig. 5
Early acute anastomosing angioid streaks of the choroid. Right eye. Case 3.

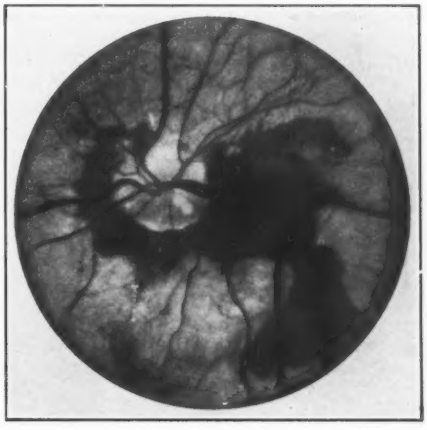


Fig. 6
Large choroidal hemorrhage, associated with angioid streaks of the choroid. Left eye. Case 3.

folding of the skin occur, such as the axillae, neck, cubital and popliteal fossae and occasionally the chest and abdomen.

"Clinically it presents faint light fawn colored, yellow reticulated discolorations seen best on stretching and relaxing of the skin, but on occasions may be so extensive that actual elevation of the skin in these areas may be noted and pinhead sized tumors observed. It rarely produces any discomfort and for the most part goes unnoticed by the patient. Since it occurs in middle or late life, it is most often considered a senile change in the skin, and for the most part clinically and pathologically resembles senile elastosis.

"Its etiology is unknown and, while it has been reported as occurring without any demonstrable change in the eye, the reports of its association with angioid streaks of the retina is observed more than a mere coincidence, so in all probability the etiology of the two diseases may be the same."

Fig. 7
Gross appearance pseudoxanthoma elasticum, associated with angioid streaks of the choroid. Case 3.

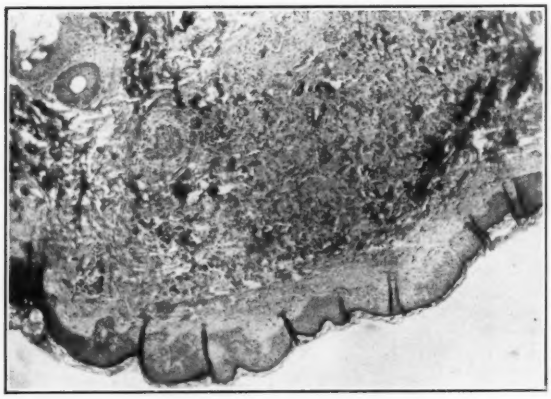


Fig. 8
Photomicrograph of skin. Pseudoxanthoma elasticum associated with angioid streaks of the choroid. Case 3.

The observation that these angioid streaks disappear on pressure, made by us in two cases and by Calhoun in a third, further substantiate the theory advanced by Clay in 1932 that these streaks are of vascular origin. The earliest findings disclose hemorrhage; streaks developed later. This indicates that the process must be acute.

In none of the 18 cases of angioid streaks studied by us have we observed the development of new streaks after the first examination. If the process were a degenerative one, streaks would continue to occur.

There is little or no evidence to support a belief in the presence of any inflammatory process. The marked choroidal atrophy seen late in the disease would support the theory of a partial choroidal venous thrombosis.

In conclusion, to summarize our observations on eighteen cases:

(1) Angioid streaks are associated with pseudoxanthoma elasticum.

(2) Angioid streaks are not associated with any other disease often enough to consider that such a disease might be a causative factor.

(3) Angioid streaks often produce no disturbance of vision. They are often found incidentally.

(4) The streaks and hemorrhages are usually located in the choroid except where hemorrhages occur in the maculae.

(5) Streaks may extend to the extreme periphery of the fundus.

(6) Angioid streaks and pseudoxanthoma elasticum do occur in the Negro race.

(7) The disappearance of recently developed streaks when the eyeball is pressed definitely proves that the streaks are vessels.*

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*Determinations of blood phosphorus and blood calcium were made by George T. Lewis, Ph.D., of the Department of Biochemistry, Emory University.

DIETHYLENE GLYCOL POISONING IN THE HUMAN*

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Although the primary object of this presentation is to record the character of disease resulting from ingestion of diethylene glycol in the human, it is also a purpose to exemplify the place which the autopsy may occupy in elucidating an unknown fatal disease and in pointing to a course for detecting the responsible factor. Further, it is desirable to emphasize and deplore the fact that many practising physicians are accepting postgraduate instruction in medicine, particularly in therapeutics, at the hands of drug manufacturers and their agents. The cases here considered represent only a few of the number of deaths resulting in the past few months from dispensing a new "elixir" preparation of sulfanilamide in diethylene glycol solvent without due regard for the effects of the menstruum itself.

Case 1.—On September 29, 1937, a Negro woman (Roper Case 94872), aged 33 years, was admitted to the Roper Hospital for retropharyngeal abscess or tumor. She gradually developed a state of anuria with coma and died on October 4. Her temperature ranged from 97 to 98.6 degrees until the morning of her death, when it rose to 100. There was a diminishing output of urine to nil in her last 24 hours. During the second day her fluid intake was 1,980 c. c., the urine output 410 c. c., and she vomited 150 c. c. During the fourth day the fluid intake was 5,030 c. c., the urine output 15 c. c. Catherized urine on October 1 and October 4 was yellow, cloudy, acid, and showed 4 plus albumin, 4 plus leukocytes, but no blood, no casts, sugar nor acetone. Her hemoglobin was 75 per cent on September 29 and 68 per cent on September 30. The blood urea nitrogen was 134 mg. and 135 mg. on October 2 and 4, while the blood creatinin on those dates was 17.6 mg. and 19.2 mg. The leukocyte count increased from 9,500 total, with 77 per cent polymorphonuclears, on September 29 to 20,400, with 79 per cent polymorphonuclears on September 30, and decreased to 7,850, with 74 per cent polynuclears, on October 2. Her blood pressure was around 100/70.

She was thought to have developed infection of the kidneys with renal failure.

An autopsy was performed two days after death, the findings of which will be given along with the other cases.

It was subsequently learned that she had been given outside the hospital on September 24 a prescription of 6 ounces of an "elixir" of sulfanilamide, but the amount taken is unknown.

Case 2.—On September 30, 1937, there was admitted a 26-months-old Negro boy (Roper Case 94881) in a stuporous state. He died in about 13 hours in what was judged to be uremia from acute nephritis. The history was that he was well until September 28, when his mother noticed that he would not talk or eat. The next morning he developed grunting, labored respiration. He had vomited once on September 29 and his bowels and kidneys had been acting.

His temperature was around 97 to 96 degrees and his blood pressure 130/110. His jaws were clenched tightly and his neck somewhat rigid. The liver was palpable 3 inches below the costal margin. The hemoglobin was 62 per cent, erythrocytes 4,345,000, leukocytes 57,950, with 81 per cent polymorphonuclears. The spinal fluid showed no abnormalities. The blood urea nitrogen was 105 mg., creatinin 6 mg., chlorides 495 mg., carbon dioxide combining power 28 volumes per cent.

An autopsy was performed on the day of death, the findings of which will be given later.

It was subsequently learned that he had been given on September 24, outside the hospital, a prescription of 2 ounces of the same "elixir" of sulfanilamide as in the previous case, for sore throat. How much he took is unknown.

Case 3.—On October 11, 1937, an 11-year-old Negro boy was admitted (Roper Case 95039) in a comatose state, to die in twenty-one hours in what was thought to be uremia from acute nephritis.

The history was that he was well until eleven days previously when he began to vomit, first only after eating. For the preceding three or four days he had been vomiting more frequently, without relation to eating. There had been no blood in the vomitus until the day before admission. He had not eaten for about a week. Drowsiness and twitching of the eyes began the day before admission.

His temperature ranged around 95 to 96 degrees in the morning of his admission day and from 100 to 98 in the evening. On the next day it was from 98 to 96 degrees. No urine was passed and a catheter in place produced only a few drops. His vomitus was bloody on October 12, his stools were tarry and he was bleeding from both nostrils. He received 1,500 c. c. of fluid by vein and 500 c. c. subcutaneously.

The hemoglobin was 75 per cent, the leukocytes 39,950, with 89 per cent polymorphonuclears, serum albumin 5.14 grams and globulin 4 grams, blood urea nitrogen 165 mg. and creatinin 12.4 mg. The spinal fluid showed nothing abnormal. The blood pressure was 142/90 and 136/90, dropping to 108/38 on the morning of his death.

The findings at autopsy on the day of his death will be presented later.

It was revealed subsequently that on October 2 he was given, outside the hospital, a prescription of 4 ounces of the same "elixir" of sulfanilamide as was taken by the previous cases, for sore throat, but the amount taken is unknown.

Following this autopsy it became apparent to the staff members concerned that something unusual had been encountered. A fourth similar case had died in the same way during the same period in the hospital and a patient with a similar case outside who was expected to die came to

*Read in General Clinical Sessions, Southern Medical Association, Thirty-First Annual Meeting, New Orleans, Louisiana, November 30-December 1-2-3, 1937.

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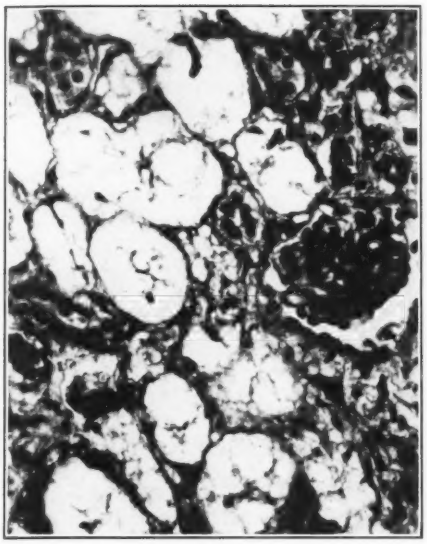

Fig. 1
Necrosis of kidney epithelium with characteristic vacuolization (No. 98481, Path. No. 42878, x 910).

attention. Histological examination of the material in hand was hurried forward, chemical examination of the tissues of the last case autopsied was instituted, the health authorities were warned that these people might have been poisoned, and an investigation for the possible causative factor was begun.

It was then learned that the case outside had been taking sulfanilamide and this new drug immediately came under suspicion, although no action of this kind had been related to it by report.

On the following day the outside case died and permission for an autopsy was secured.

Case 4.—This was a Negro (Path. No. 43162) man of about 30 years, who had developed dizziness, nausea, epigastric pain and vomiting about October 8. On October 10 he was in a state of anuria and catheterization of the bladder produced only blood and pus. On October 13 permission for a blood examination was secured. The hemoglobin was 69 per cent, the leukocyte count 26,750, with 93 per cent polymorphonuclears, the blood urea nitrogen 127 mg., blood creatinin 13.8 mg., and blood sulfanilamide 1.5 mg. (therapeutic level believed to be about 10 mg.). His blood pressure and temperature readings are not available. He died in a state of apparent uremia.

Upon this autopsy there was further assurance that we were dealing with a lethal poison of particular influence on the kidney.

It was then learned that the sulfanilamide preparation taken by this man was an elixir, so labeled, and a sample of the drug was secured. He had taken 4 ounces between October 6 and about October 8.

As the investigation to determine whether the previous cases had taken the same drug was started, the lay press story broke revealing apparently like occurrences in other places, all from the same so-called "elixir of sulfanilamide," and disclosing that the menstruum used contained dyethylene glycol, about 72 per cent by volume, with about 40 grains of sulfanilamide to the fluid ounce, according to a reported test at the laboratory of the American Medical Association.[1]

The connection among our cases then was established and the amounts prescribed (from the same container) were learned, as previously given.

It is not thought that the sulfanilamide was the responsible agent. In fact, the blood content of that substance determined in one case is well below the reported therapeutic level, although this examination was done about five days after he probably took the drug. It appears that the lethal substance was diethylene

1. Editorial: Deaths Following Elixir of Sulfanilamide Massengill. J.A.M.A., **17**:1367 (Oct. 23) 1937.

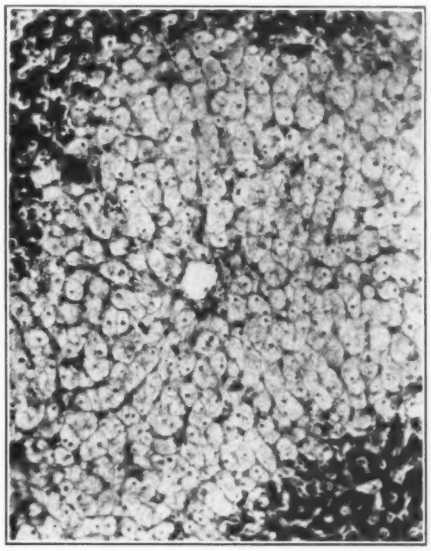

Fig. 2
Central lobular necrosis of liver with characteristic vacuolization (Path. No. 43162, x 260).

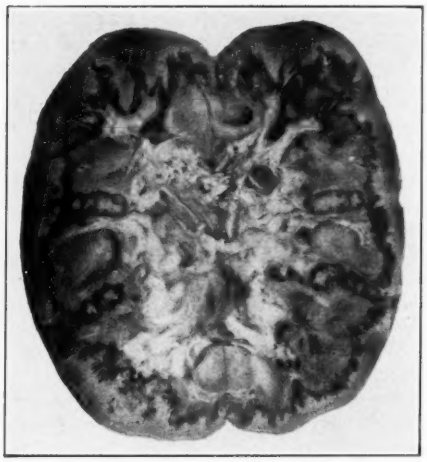

Fig. 3
Massive cortical necrosis of kidney (Path. No. 43162).

glycol, apparently used by the manufacturer simply as a solvent for the sulfanilamide.

Study of the autopsy material from these cases reveals an interesting and somewhat unique picture, similar to that produced by certain other poisons and yet apparently distinct. They may be summed up as showing in common a characteristic acute necrosis of the secretory tubules of the kidney and an equally characteristic central lobular necrosis of the liver, both conditions apparently based on direct epithelial damage. In addition, two cases showed infarction of the kidney cortex, in one complete in both organs, like embolic infarction and apparently resulting from vascular closure in the areas affected. In at least one case, the boy who vomited blood, there was an acute gastritis in which the stomach glandular epithelium suffered damage comparable to that in the kidney and liver. Unfortunately the nature of the material is not such as to allow determination as to whether this was a condition common to all. They all had an early acute lobular pneumonia by the time of death.

No examination of the brain or cord was made, and no other relevant organic changes were revealed. A detailed description of the kidney and liver changes and such data as is considered worthy of the space follows:

Kidney.—These organs were enlarged in all cases, markedly in the man, the 26-months-old boy and the woman, not conspicuously in the 11-year-old boy. In this last, except for suspicion already cast on the kidneys, they probably would have passed grossly as of a mild grade of cloudy swelling. However, both of his kidneys contained small typical fresh white infarcts, for which there was no satisfactory explanation.

The kidneys from the man were very striking, markedly swollen, the cortex white and soft, including the inter-pyramidal columns, and sharply separated from the pyramids by a jagged zone of hemorrhage. The appearance was of recent anemic infarction of the whole cortical area. In the other two cases swelling and some cloudy pallor was all. None showed any yellow discoloration.

Histologically the changes common to all consist of extreme degeneration, necrosis and disintegration of the epithelial lining of the secretory portion of the tubules. In the cortex, only the fringes of which remain intact in the man's kidney, the characteristic change is seen, particulary in the tubules of large caliber, although small ones are also involved, and in the straight tubules in the medullary rays and down into the pyramids; more or less the whole secretory portion apparently. This consists of extreme distention of the cells, to block the lumen, the rims usually distinct, the cytoplasm converted into a thin, almost clear, network of fine fibrillar and granular substance, the nucleus characteristically pyknotic, small, shriveled, dense, and commonly displaced to or near the rim. The lining of the space of Bowman shows varying grades of this change. In addition to this striking feature the cells of some tubules show only swelling and granularity of cytoplasm, with nucleus intact. In other tubules more or less of the whole lining is cast into a granular debris, while in the kidneys of the woman and the 11-year-old boy masses of necrotic material in many tubules show the basic staining qualities of calcification as in bichloride of mercury poisoning. Where there is conspicuous free necrotic material in the tubules, it is usually accompanied by polymorphonuclear leukocyte collection. In still other tubules of the cortex, particularly in the case of the woman, who lived about ten days after taking the drug, the epithelium appears to have lost cytoplasm on the lumen side and to have become flattened into ovoid or spindle form.

In the pyramids certain straight tubules, apparently the duct portion, and some of small

caliber in the cortex have not suffered extremely, the cytoplasm showing some granularity and minor vacuolization only. These tubules and some others in the cortex, usually the less damaged, contain albuminous casts, and while the spaces of Bowman are free and clear in the majority, some contain granular material.

In the two cases without infarction the blood vessels, including the glomerular tufts, are apparently in good order and open, although in all kidneys the intertubular small vessels in the pyramids are markedly congested, this being more pronounced at the base of the pyramids in the zone where vascular closure occurred in the infarction in two.

Likewise in other organs there is no evidence of vascular damage except that in the spleen of the 11-year-old boy, who had definite hypertension until the day of death, some of the malpighian arterioles show marked hyaline thickening of the inner coat.

Typical anemic infarction of the cortex occurred in the kidneys of the 11-year-old boy and of the man. In the former there were several small ones, about four millimeters or less at the base in the cortical surface, with the apex about the junction of cortex and medulla. These were of the white appearance, with surrounding zone of hemorrhage, characteristic of embolic infarcts. In this zone the glomerular capillaries and other small vessels are closed by fresh thrombi.

In the kidneys of the man the infarction encompassed the entire cortex and the interpyramidal columns, where all structures are completely dead, the surrounding zone of hemorrhage following the base line of the pyramids and dipping down to the bottom of Bertini's columns, leaving only the pyramids and the fringes of the columns to show the intact tubules and their characteristic cellular changes.

Following the base line of this infarction apparently all vessels are blocked by thrombi, including arteries of fair size, veins and capillaries. Here are a few arterial branches with lumen remaining open, showing the intimal cells vacuolated and polymorphonuclear leukocytes scattered throughout their coats. The whole picture is that of complete vascular closure at the junction of cortex and medulla.

Since there are no such vascular changes elsewhere, and since they did not occur in the other two cases, it appears that this feature is a secondary one, perhaps dependent upon the toxic necrosis in the nephrons, although the mechanism of production is not clear at present.

Liver.—In all cases the liver was moderately enlarged, the woman's liver weighing 2,000 grams and being the most conspicuously enlarged. In all cases it was pale, but not yellow, particularly immediately about the central venules.

Histologically all are alike in showing a strictly limited central lobular zone necrosis.

Here the cells are markedly swollen, the rims usually preserved, the cytoplasm converted into an almost clear network of fibrils and granules, the nucleus shriveled, dense, and usually centrally placed, a picture quite like that in the kidney epithelium.

While there is an occasional cell of this order in the outer zone, the cells there are in good order by contrast, showing commonly merely some cytoplasmic granularity.

In the woman's liver in a few lobules the cells of the central zone are shriveled and granular, with pyknotic nuclei, and some are breaking up, instead of being swollen and clear.

The central venules are open and all other structures are apparently in good condition.

Scarlet red staining for fat and carmine stain for glycogen revealed that these substances were not responsible for the cytoplasmic disruption in kidney or liver.

Stomach.—Neither the stomach nor intestine showed grossly any evidence of abnormality except in the 11-year-old boy, and thorough microscopic study of this system was neglected in the other cases. The boy's stomach exhibited grossly some congestion of the mucosa and histologically showed a definite acute gastritis. Here the surface and gland mouth epithelium is lost, the capillaries in the mucosa are quite engorged, and the epithelial cells deep into the glands, including the acid cells, show fragmentation and vacuolization of the cytoplasm, with occasional pyknotic nucleus, suggesting the kidney and liver cell damage. The mucosa of the remainder of the tract was normal.

No other gross or microscopic abnormalities were encountered, except that all had acute lobular pneumonia at the time of death, and the woman had syphilitic cirrhosis of the liver, with gumma, enlargement of the spleen from portal congestion, and gumma of the pharynx.

A GENERALIZED CASE OF MORPHEA GUTTATA*

By HOWARD HAILEY, M.D.†
and
HUGH HAILEY, M.D.‡
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The rarity of generalized morphea guttata is attested by the occurrence of one case in an estimated thirty thousand dermatologic patients seen during the past sixteen years. There is a paucity of literature on the subject. This is not true of circumscribed scleroderma or morphea.[1 2 3] Neither is the latter condition rare.

An equanimity of opinion as to the clinical and histological appearance of morphea guttata is not to be found.[4 5 6 7 8] In reviewing the literature, one notes a reported case of morphea guttata described in such a fashion as to be an excellent example of circumscribed scleroderma or morphea or white-spot disease.

If the descriptive term, guttata, is to be retained in dermatologic texts, it should be restricted to those clinical types of morphea which are characterized by "drop-like" lesions.

Probably the time has arrived when the clinical types of scleroderma should be described and classified by a committee of textbook authors.

There is a marked similarity in the histological picture of all clinical types of scleroderma, provided the biopsy is taken of lesions exhibiting comparable phases in the pathologic process.

CASE REPORT

Mrs. G. L. F., a white woman, aged 50, came in for examination first on July 26, 1934. At that time she complained of an eruption involving her body in general, having a duration of two months. She stated that the lesions appeared first on her shoulders and chest. Gradually, over a period of two months, the eruption had become general. She had experienced no burning, tingling or itching to forewarn her of the approach of new or developing lesions. They first were seen as small pinhead skin-colored pimples which gradually enlarged to the size of a pea. The lesions had remained discrete and were persistent. She had felt no alarm about her condition, for her general health she thought to be excellent. Her only reason for seeking medical attention was the skin eruption. No information pertinent to the present complaint was elicited from the family and past history of the patient.

Examination of the skin showed a skin-colored symmetrically arranged papular eruption involving the entire body, neck and extremities, except the palms and soles. A few lesions were present on the eyelids and

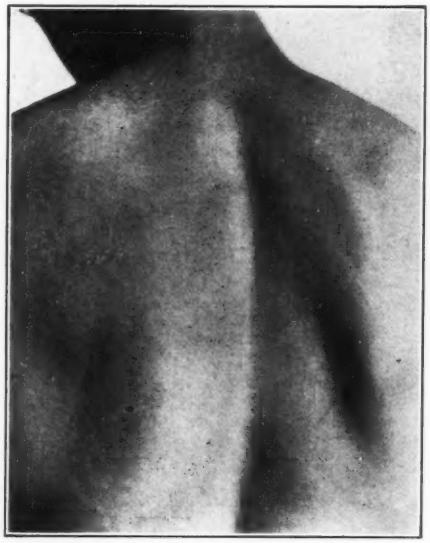

Fig. 1
Lesions over back.

Fig. 2
Lesions inside right arm.

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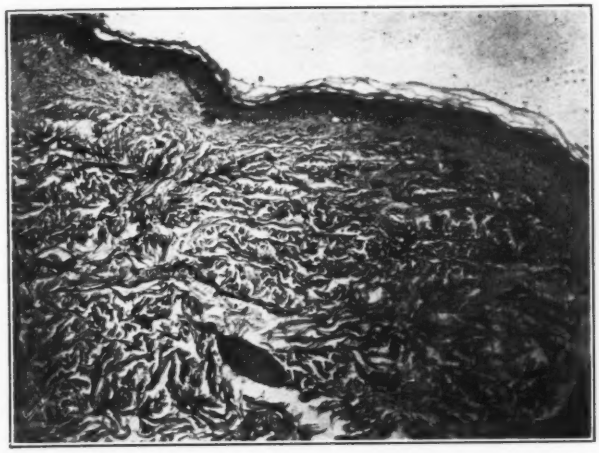

Fig. 3
Photomicrograph showing absence of papillae, hypertrophy of collagen and small amount of cellular infiltration.

lower part of the face. None was seen on the scalp. The lesions were discrete and while there was a very large number of lesions over the neck, body and extremities, no evidence of coalescence was present.

The individual lesion is circumscribed, elevated and varies in size from a pinhead to a pea. Its color is that of the contiguous normal skin. Pigmentation, telangiectasis and excoriation are absent. On palpation, a decided infiltration is noted. The follicular openings over the lesions are more prominent than those in the intervening skin. Friction of the skin brought no response from the lesions and dermographism could not be demonstrated. Still on inspecting the eruption from a distance, except for color, the picture presented strongly suggested a generalized urticaria.

Physical examination revealed no information related to the eruption and supported the patient's belief that she was in good health. There was a rapid increase in pulse rate, and the blood pressure was 170 systolic and 110 diastolic, which was thought to be due to nervousness as a result of the examination. Repeated examinations of the urine were negative. The Wassermanns and provocative Wassermanns of the blood were negative. The basal metabolism reading was plus 16 per cent. Examination of the blood showed 90.9 milligrams sugar, 31.5 milligrams nonprotein nitrogen, 1.5 milligrams creatine, and 142.8 milligrams cholesterol. The study of the blood cells revealed no evidence of hemoblastic infiltration of the skin. Sections obtained by biopsy were reported to show the characteristics of early morphea.

The patient referred to has been under observation for three years and four months. She was in the office three weeks ago. At that time the clinical picture was the same as when she was first seen.

Abstracts of the literature dealing with morphea guttata were purposely not incorporated in this report. The accompanying references may be of aid to those interested in this subject beyond the case herein reported.

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DISCUSSION (*Abstract*)

Dr. Leslie M. Smith, El Paso, Tex.—Dr. Hailey has presented a case of a very unusual type of scleroderma, for, after all, morphea guttata is properly regarded as a variety of scleroderma. I have not personally seen a case of the generalized guttata variety and, judging from the literature, it is exceedingly rare. The fact that there are many theories of the cause of scleroderma is proof enough that the real cause is unknown. The endocrine glands and metabolism, however, seem to offer the most promising fields for study. Practically all the endocrines have been accused of playing a part in the etiology of scleroderma. The disease has been found in connection with both hypo- and hyperthyroidism, and cases have been reported benefited by the administration of thyroid extract. Other cases have been benefited by injections of posterior pituitary extract. Quite commonly there is found in scleroderma a retention of calcium, with a decreased urinary calcium output. Some cases have improved on large doses of viosterol (200,000 to 300,000 units daily), and the urinary excretion of calcium has increased coincidentally. Possibly there is a hyperparathyroidism in these various forms of scleroderma; at least there is a disturbed calcium metabolism in many cases. I am sorry Dr. Hailey did not report on the calcium metabolism in this case. He did, however, find an increased basal metabolic rate along with other evidences of a slight hyperthyroidism. It would be interesting to observe the course of the morphea under treatment with Lugol's solution or possibly radiation therapy to the thyroid.

Dr. J. Lamar Callaway, Durham, N. C.—As Drs. Hailey have pointed out, there is perhaps no clinical entity today which presents as much diversity of opinion as does morphea guttata. In Unna's original description of "white spots disease," he probably described the clinical picture as presented today by Drs. Hailey. I am

in hearty accord with the Drs. Hailey's feeling that "white spots disease" as generally discussed today, which includes morphea guttata, lichen sclerosis atrophicans, lichenoid scleroderma, cardboard scleroderma, and so on, should be carefully studied and completely reclassified. It appears likely, however, that we shall continue to grope in the same old darkness because many of the cases we see present certain characteristics that are in common with lichen planus, while other cases present characteristics that appear more often in the scleroderma group. Of the more recent writers Miescher is of the opinion that the disease should be rightly called not morphea guttata, but lichen sclerosis atrophicans, and points out that it is clinically and histologically a well defined entity wholly and completely separate from scleroderma with much more resemblance to lichen ruber planus than to any of the scleroderma group. Sellei, on the other hand, maintains that on the basis of his observations morphea is not an independent disease at all, but a form of scleroderma and the small glistening white spots, "white spots disease," or morphea guttata, are sequelae of the smaller sclerodermic changes, but should be differentiated from the true morphea. MacKee and Wise have taken the middle course, saying that all recorded cases of "white spots disease" can be divided into two groups, a scleroderma group and a lichen planus group. As has already been pointed out, the white color is as a rule particularly striking. In the patient presented by Drs. Hailey the extreme whiteness was not an outstanding characteristic, but the distribution, chronicity and histological examinations have established the diagnosis satisfactorily in this case. In addition to the white color, the lesions may be papular or even depressed. They may be firm cardboard-like infiltrations or may be completely relaxed. Itching may or may not be present. The lesions spread by discreet, isolated dissemination, being particularly prominent over the back, chest, wrists, and neck as a rule. The course is extremely chronic, though there may be complete regression without atrophy. In the majority of the cases, however, atrophy is present. As a rule, the histological picture presents some four or five outstanding characteristics, notably, atrophy of the epidermis with disappearance of the papillary body and hyperkeratosis. Secondly, the subepidermal connective tissue infiltration with inflammatory cells and comparatively few nuclei present due to the sclerotic connective tissue. Thirdly, loss of elastic tissue. Fourthly, round cell inflammatory infiltration with some edema around the basal cell layer. It should be emphasized that there is always hyperkeratosis and never parakeratosis and the characteristic findings are usually found in the cutis and not in the epidermis. As far as treatment is concerned, I offer one suggestion: that of the use of a ketogenic diet plus the use of ammonium chloride to increase the ketosis. I hope that the presentation of this unusual case by Drs. Hailey will serve as a stimulus for some one to attempt a clarification of this morphea guttata problem, for to me at least the etiology is far from clear.

Dr. Hailey (closing).—Various treatments were instituted in this case of morphea guttata, but there has been no change in the eruption. We hope to be able to report on it several years hence.

AN INQUIRY INTO THE NATURE OF SO-CALLED SYNCYTIOMA*

A RECONSIDERATION OF CHORIONEPITHELIOMA

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and
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Augusta, Georgia

INTRODUCTION

Confusing intra-uterine pathologic processes are frequently observed after abortion, retained placental tissue, hydatid mole or destructive placental polyp. These pathologic conditions are difficult to classify and, because they assume certain neoplastic features, occupy a place somewhere between an exaggeration of physiologic trophoblastic activity and chorionepithelioma. These processes are generally interpreted as types of chorionepithelioma. From our experience as well as from a review of the literature on this subject, we believe that the frequency of chorionepithelioma is greatly overestimated. There seems to be a lack of unanimity as to what histologic, biologic or clinical criteria constitute a diagnosis of this dreaded disease. Many of the reported cases would be classified by us as syncytial cell hyperplasia, retained hydatidiform tissue or invasive moles. The erroneous conceptions regarding the nature of the highly malignant chorionephithelioma and the great variations in its reported incidence may be due to an insufficient appreciation of the structure and physiology of chorionic epithelium. This fact led Emil Novak[1] to remark:

"There is no field in gynecologic pathology in which mistakes are more readily made."

GENESIS OF THE PROBLEM

In 1905, Marchand expostulated upon the fetal origin of this capricious neoplasm. He changed the then existing concept of Saenger, who had labeled it "deciduoma malignum," a nomen which inferred a purely maternal origin. Marchand further recognized two groups of chorionepitheliomas, the atypical and the typical. In the atypical group he placed those growths in which there was an extensive infiltration of the decidua and myometrium with isolated cells which he identified as syncytial wan-

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*From the Department of Pathology and Department of Gynecology, University of Georgia School of Medicine, Augusta.

dering cells. Schmauch,[2] in 1907, in an exhaustive review of 206 cases, noted a correlation between histologic structure and the clinical course of the disease. He took cognizance of the cellular components of these growths, namely, Langhans' cells, syncytium, and syncytial wandering cells. He recognized the apparent harmlessness of the atypical chorionepithelioma of Marchand as compared with the highly malignant nature of his typical chorionepithelioma, and to Marchand's classification he added a transitional form of intermediate malignancy. In this type he noted a preponderance of large syncytial cells besides Langhans' and syncytium. Schmauch's work paved the way for Ewing's[3] masterful interpretation of the problem in 1910. Ewing recognized that there existed anatomical and clinical distinctions between destructive moles, typical chorionic carcinoma and atypical degenerating tumors. He proposed the terms "chorio-adenoma," "chorio-carcinoma" and "syncytial endometritis" as subdivisions of chorionepithelioma. This belief has been shared by many students of the subject (Rosenzweig,[4] Mathieu and Palmer,[5] and others). A sane and judicious use of Ewing's classification has been of inestimable worth in evaluating the basis for operative interference. Unfortunately, however, the classification is all-embracing and the indiscrete use of it has permitted the accumulation of an extensive literature in which the true incidence of chorionepithlioma has been greatly beclouded.

INCIDENCE OF CHORIONEPITHELIOMA

The questionable incidence of chrorionepitheliomas that are said to follow hydatid moles has added further to the confusion and has varied from 31.4 per cent (Findlay) to less than 1 per cent (Novak). An analysis of numerous reported cases of chorionepitheliomas which followed hydatid moles failed to convince us of the neoplastic character of many. Lazar and Kliman[6] recently reported four cases of chorionepithelioma. Using Ewing's classification they designated two of these as syncytioma, one as syncytial endometritis and one as chorio-adenoma destruens. All of these followed hydatid moles and consequently they felt that their experience was in accord with that of most observers, that about 15 per cent of hydatid moles are followed by chorionepithelioma. This conclusion was far different from the experience of Sherman,[7] who, in a report of seventy-eight cases of hydatid mole, stated that there was only one case of chorionepithelioma in 196,399 obstetric and gynecologic patients at the New York Lying-In Hospital, and this one did not follow hydatid pregnancy. Hitschman and Cristofoletti studied a series of 200 hydatid moles in which 7.5 per cent resulted in chorionepithelioma. Teacher regarded this as a high percentage and, because all recovered after operation, he questioned the validity of the diagnosis of malignancy. We have never encountered a true chorionepithelioma in a female in some 31,000 surgical specimens which included twenty-one hydatid moles. But in some of the uteri removed after expulsion of a mole, we have noted an invasion of the myometrium by chorionic elements.

PURPOSE

The question of the great discrepancy in the incidence of this disease naturally arose. The distribution and occurrence could not be due altogether to racial, climatic or geographic factors. It appeared that the marked variation was due to an academic *impasse,* a lack of universal agreement of terminology, and a difference of interpretation of the histologic considerations of the problem.

The purpose of this paper, through the presentation of a series of case reports, is: (1) to inquire into the nature of the so-called syncytioma of Ewing. (2) To emphasize the fact that many of the conditions designated as syncytial endometritis or atypical chorionepithelioma are not true tumors, but represent an exaggeration of the syncytial reaction of pregnancy. (3) To take cognizance of the suggestion by Frank and Geist[8] that the syncytioma of Ewing on one hand, merges with the non-neoplastic pregnancy reaction, and on the other hand with transitional types of chorionepithelioma. (4) To deprecate the wanton interpretations of a most valuable procedure in the diagnosis of chorionepithelioma, namely, the biologic pregnancy test.

HISTOLOGIC CONCLUSIONS

We have studied histologic sections of chorionepithelioma, hydatid mole, invasive mole, destructive placental polyp, and so-called syncytial endometritis and syncytioma obtained from many sources throughout this country and Canada. The cellular components entering into these processes are divisible into six groups. These are illustrated in *Chart 1.* The Langhans' cells are small, clearly defined, faintly basophilic, polyhedral shaped cells. The nuclei are vesicular, contain finely dispersed chromatin granules and prominent nucleoli. We have coined the term metasyncytium to denote nests of cells which are derived from and which appear to be a later stage of Langhans' cells, and

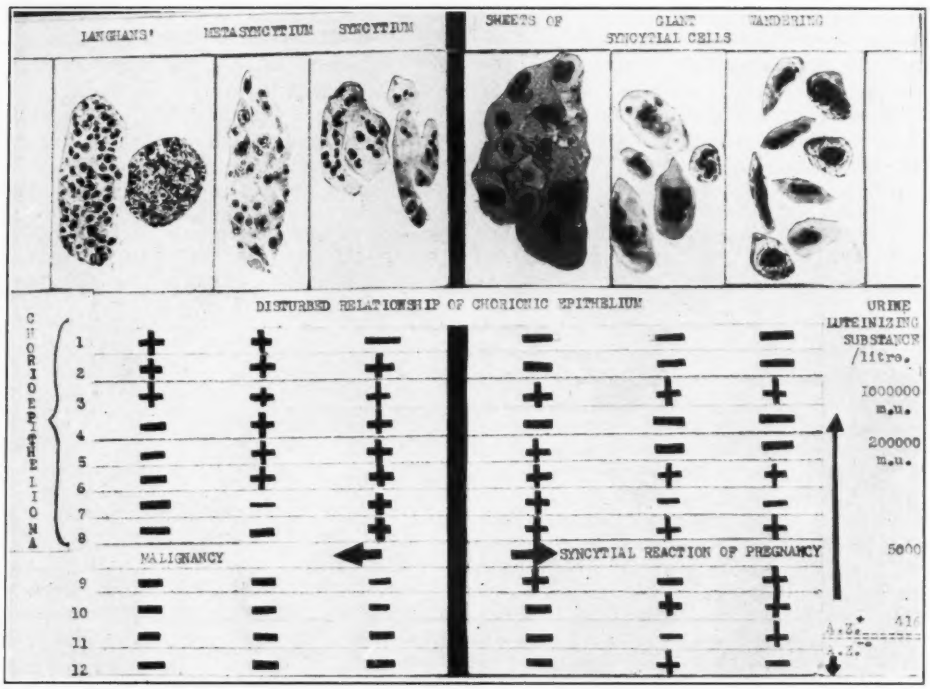

Chart 1

The cellular components of tissue sections suspected as chorionepithelioma (excluding invasive moles) may be grouped to the left or right of an imaginary line. Twelve possible variants are charted, eight of which are considered malignant. The slightest shift to the left of the line permits a diagnosis of chorionepithelioma. A complete shift to the right to the exclusion of cells to the left, permits a diagnosis of benign syncytial hyperplasia. Indicative of great malignancy is the degree of Langhans' cell proliferation (without attachment to villi for nourishment), and this is usually paralleled by corresponding levels in the quantitative biologic hormone assays.

to which they bear a close resemblance. These metasyncytial cells are faintly acidophilic and tend to cohere. The nuclei are vesicular, slightly hyperchromatic, and the dispersion of chromatin is course. The syncytium occurs as a plasmodial ribbon-like mass of acidophilic, vacuolated protoplasm which contains several scattered nuclei. No cellular boundaries are visible. The syncytial cells may occur in nests of individual cells, as giant cells or as isolated wandering cells. The sheets of syncytial cells are composed of voluminous "decidua-like" cells with bizarre, hyperchromatic nuclei. The giant syncytial cells are large multinucleated cells. The nuclei are small and are piled up haphazardly in the central portion of the cell. Karyorrhexis and karyolysis indicate impending cell dissolution. The syncytial wandering cells are isolated, oddly shaped, deeply stained, irregularly mononucleated cells.

We have found that whenever there is deep invasion of the uterine musculature by trophoblastic cells (unconnected with villi) the diagnosis resolves itself into two possibilities, namely, malignant chorionepithelioma or benign syncytial hyperplasia. The occurrence of villi precludes either a diagnosis of retained products of conception, hydatid mole or placental polyp. The latter two may be either simple or invasive. The presence of villi excludes these processes from consideration as chorionepithelioma *per se*. We are disposed to think of the invasive mole or the destructive polyp as malignant hydatid moles. The malignancy is only relative, that is, only locally destructive and locally malignant. Metastases are rare and these are considered rather as deportations which usually regress.

In *Chart 1* we have endeavored to demonstrate that the trophoblastic cellular components of any tissue section under study may be grouped to the left or right of an imaginary line (central black line in the chart). At least twelve possible

variants have been observed and these are exhibited in the chart. The slightest shift to the left of this line permits a diagnosis of chorionepithelioma, and the greater the shift to the left, the greater the malignancy. On the other hand, a shift to the right to the complete exclusion of cells on the left of the line permits a diagnosis of benign syncytial hyperplasia. Whenever the cellular components fall on either side of the central dividing line, the relative malignancy may be gauged from the shift to the left or right. When Langhans' cells are capable of independent growth (without attachment to any villous processes for nourishment) and are capable of preserving their identity in a foreign environment, it is evidence of their complete autonomy and their malignant propensities. When the invasive trophoblastic cells appear as voluminous cells, whether in sheets, as isolated cells or giant cells, exhibiting phases of degeneration, it is evidence of decadence, of ended cell life, of complete subordination to the host.

HORMONE STUDIES

It is essential that histologic interpretation go hand in hand with biologic hormone studies. It is by the fullest use of the methods at our command that the vagaries of trophoblastic activity may be understood. Perhaps in this manner we may be capable of determining where the exaggerated syncytial reaction of pregnancy ends and chorionepithelioma begins. A qualitative Aschheim-Zondek reaction following abortion or expulsion of a hydatid mole may merely mean retention of living chorionic elements and not necessarily the development of "early" chorionepithelioma. Brindeau and his associates[9] have pointed out that because of the prolonged period of hormone elimination the consequent persistence of a positive Zondek reaction does not necessarily indicate the malignant evolution of the molar rests. Zondek[10] has recently demonstrated that the pregnancy test may remain positive from four to twelve weeks after the discharge of a mole. If, after six weeks, the content of gonadotropic substance in the urine progressively increased, it was suggestive of a diagnosis of chorionepithelioma, particularly if a positive reaction was also obtained with spinal fluid. For confirmation of the diagnosis he advised exploratory curettage. If the result of the histologic examination was doubtful, the result of biologic assay of the urine and the spinal fluid was of great significance. In case the pregnancy test became negative after the discharge of a mole and then once more became positive within some time, Zondek advised the possibility of either a new pregnancy or a chorionepithelioma. The hormonic diagnosis of chorionepithelioma may be established when at least 416 m. u. (up to 1,000,000 m. u.) of luteinizing substance per liter of urine are present, provided a new pregnancy was excluded.

The following case reports are presented to illustrate the problem at hand.

THE SYNCYTIAL REACTION OF PREGNANCY

Case 1.—A white female, aged 28, entered the University Hospital for a prophylactic termination of a four to five months' pregnancy. The method of election was by cesarean section and the uterus was emptied of its contents. Bleeding from the uterus, however, could not be controlled and a supracervical hysterectomy was then performed. Histologic study of sections from the uterus revealed an invasion deep in the musculature by large syncytial wandering cells (*Fig. 1*). This is a somewhat exaggerated syncytial reaction of pregnancy and may have been responsible for the excessive bleeding.

The physiology of the wandering syncytial cells in pregnancy is unique. The remarkable extent to which these cells may invade the uterine wall in normal gestation has been emphasized by many observers and especially Meyer. In a normal pregnancy these cells penetrate the

Fig. 1 (Case 1)
Syncytial reaction of pregnancy. The elongated syncytial wandering cells with hyperchromatic nuclei are lying deep in the myometrium.

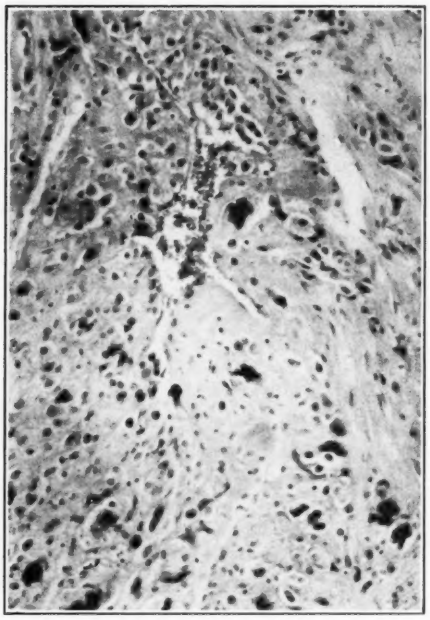

Fig. 2 (Case 2)
Exaggerated syncytial reaction of pregnancy following abortion. Note the multinucleated giant syncytial cells.

walls of veins and may be found in the pulmonary veins. Schmorl has observed this in 80 per cent of 150 eclamptics studied at autopsy.

EXAGGERATED SYNCYTIAL REACTION OF PREGNANCY FOLLOWING ABORTION (THE SYNCYTIAL HYPERPLASIA OF GEIST)

Case 2.—A 32-year-old married woman was admitted to the Buffalo General Hospital* with a history of having missed two menstrual periods. Two weeks previously she began to pass clots. The uterus was the size of a three months' pregnancy. A fetus of approximately three months was found in the vagina. The patient was discharged three days after curettage. Histologic study of curettements showed an extensive invasion of the uterine musculature, the walls and lumina of veins by syncytial wandering cells and multinucleated giant cells (*Fig. 2*). A Friedman test was negative four weeks later.

This case study and the histologic findings are almost identical with the case of exaggerated syncytial reaction recently reported by Choisser and Notes.[11] We are in perfect agreement with these authors that

"the histologic differentiation of atypical syncytial reaction from true chorionepithelioma is frequently difficult and often the distinction can be made only on the basis of gonadotropic hormone studies."

However, we fail to agree with their histologic interpretation of

"invading Langhans' cells hanging in clusters within the vessel lumen."

We regard these clusters of cells as syncytial.

SYNCYTIAL CELL HYPERPLASIA FOLLOWING A COMPLETE ABORTION (SYNCYTIAL ENDOMETRITIS OF EWING)

Case 3.—A white married woman, aged 27, was admitted to the Montreal Jewish General Hospital* complaining of the passage of clots which had suddenly commenced one day previously. She was a para 2, gravida 3. Her last menstrual period occurred three months previously and was normal in all respects. The uterus approximated in size a three months' pregnancy. On the date of admission a curettage was performed. Histologic examination revealed an invasion of the decidua, myometrium and veins by numerous large hyperchromatic syncytial wandering cells and giant syncytial cells (*Fig. 3*), which aroused suspicion of chorionepithelioma. Consequently a Friedman test was performed which proved negative. Roentgen ray studies of the lungs showed no evidence of metastases. She was discharged on the eighth day. She was readmitted two weeks later with an interval history of spotting almost daily

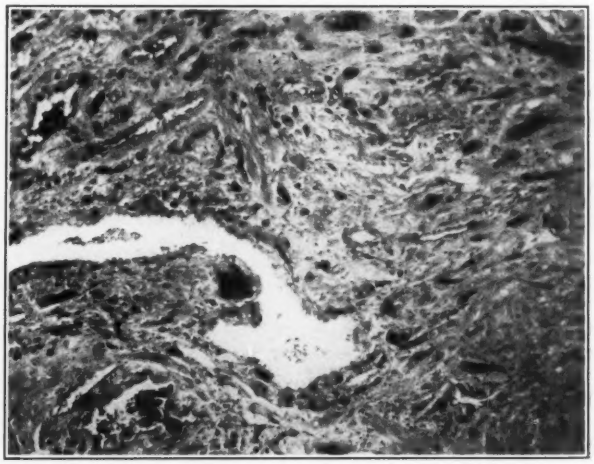

Fig. 3 (Case 3)
Syncytial cell hyperplasia following complete abortion. Note the invasion of the myometrium and the encroachment of veins by syncytial wandering cells and giant syncytial cells. Note the syncytial cells in the vein (left lower corner).

*We gratefully acknowledge the cooperation of K. Terplan and S. Sanes in providing us with four case histories and sets of histologic sections for use in this study, of which this is one.

*We are indebted to Dr. L. Spector for the privilege of including this case report in our study.

since her discharge from the hospital. The retroflexed uterus was still larger and softer than normal and the right ovary was palpable. The lungs were again rayed and no evidence of metastases was seen. The Friedman test was repeated and it was negative. Another curettage was performed and the pathologist reported:

"Bits of myometrium and resting endometrium; there are no decidua cells or chorionic tissue."

The use of the urine pregnancy test in this case amply demonstrated the value of this procedure in preventing serious error. Dietrich describes the case of a young woman in whom histologic diagnosis of chorionepithelioma had been made. As the pregnancy test remained negative at repeated intervals, no operation was performed. The hormonic urine assay demonstrated the incorrectness of the histologic diagnosis and the young woman, who has remained perfectly well, was saved from a mutilating operation. In contrast, however, the report of Schumann and Voegelin[12] must be mentioned, in which histologic diagnosis of two curettements were inconclusive and because of two negative Friedman tests, operation was delayed. Four months later the patient had a massive hemorrhage, the Friedman test was now strongly positive and a hysterectomy was performed. A typical chorionepithelioma was found on histologic examination. The patient died of cerebral metastases five months later. This is an example in which failure of biologic tests (however rare) places added importance upon diagnoses offered by careful histologic study.

SYNCYTIAL HYPERPLASIA (SYNCYTIOMA OF EWING)

Case 4.—A white female, aged 48, gravida 15, and three months pregnant, was admitted to the Notre Dame Hospital,* Montreal, complaining of uterine bleeding of two months' duration. Two days after admission she aborted a complete fetus. Two weeks later a total hysterectomy was performed on the suspicion of a hydatid mole. The uterus was large and soft. Histologic report (by Louis-Charles Simard): "The internal surface of the uterus is covered by a fibrino-purulent mat. Here and there are giant syncytial elements and the underlying muscle is infiltrated by numerous decidua-like cells. The latter are at times voluminous and monstrous. It may be thought that this is a chorionepithelioma, but these decidua-like figures are found so frequently in the debris of retained placental tissue that it cannot be a question of malignancy. Besides, the history of the patient does not lend itself to such an eventuality."

*This case report as well as the histologic interpretation are herein included through the courtesy of Louis-Charles Simard.

The histopathologic interpretation of the case by Simard reveals a thorough understanding of this problem, with which we are in complete accord. The older authors such as Saenger thought the decidua-like elements to be maternal in origin. Schmauch emphasized the fact that "the so-called decidual islands are possibly nothing else than advanced, hypertrophic, trophoblastic cells" for which Minot had suggested the term "hypertrophic degenerated trophoblastic cells." The nuclear fragmentation, so evident in *Fig. 4,* is indeed evidence of cellular degeneration. The invasiveness and lytic effect of these cells upon the surrounding uterine tissue further bespeak their trophoblastic origin (*Fig. 4*) in spite of their resemblance to decidua cells. We have recently had occasion (through the courtesy of R. A. Lyon) to study the morphology of masses of decidual cells in deciduomas experimentally produced by traumatizing the nonpregnant horn of the uterus of a pregnant rat.[19] The strictly localizing nature of these growths stood out strikingly in comparison with the invasive and degenerative features of syncytial cells.

SYNCYTIAL HYPERPLASIA FOLLOWING HYDATID MOLE (SYNCYTIAL ENDOMETRITIS: SYNCYTIOMA OF EWING)

Case 5.—A colored female, aged 22, gravida 4, was admitted to the University Hospital complaining of uterine bleeding and labor pains. Soon after admission she passed a hydatid mole. Bleeding began after two months of amenorrhea and has continued irregularly for one month. Histologic examination of the specimen revealed hydropic villi with pronounced epithelial proliferation, particularly of the syncytial layer. The patient continued to bleed and a curettage was performed twelve

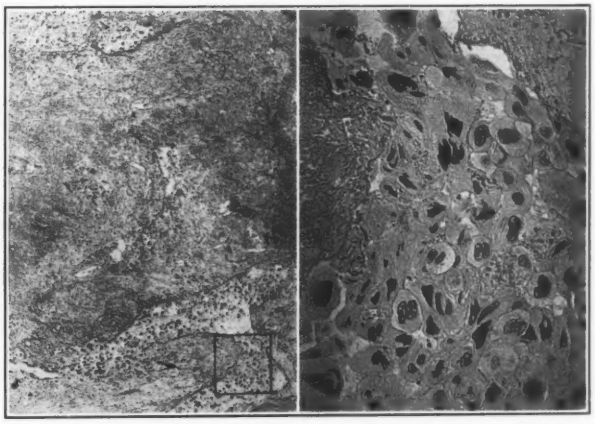

Fig. 4 (Case 4)

Syncytial hyperplasia (syncytioma of Ewing). Low and high power photomicrograph. Note the sheets of individual syncytial cells. The cells are voluminous, and exhibit nuclear fragmentation and hyperchromatism.

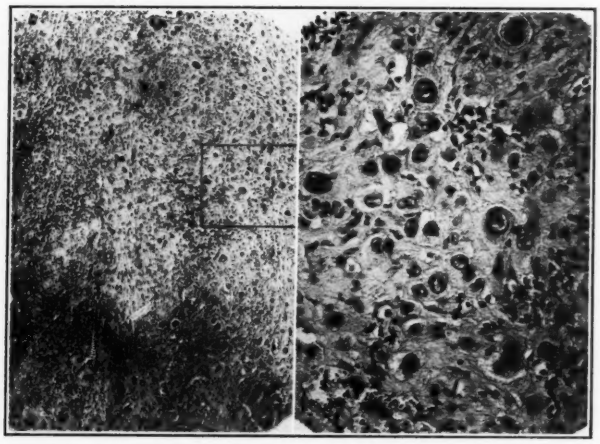

Fig. 5 (Case 5)

Syncytial hyperplasia following hydatid mole (syncytial endometritis, syncytioma of Ewing). Low and high power photomicrograph. Note the diffuse invasion of the myometrium by hypertrophic syncytial wandering cells and giant syncytial cells. Note the accompanying inflammatory reaction.

days after discharge of the mole. Hemorrhage was brisk following curettage and again during the following day, necessitating packing. Histopathologic examination of the curettements revealed no chorionic villi. A diffuse invasion of the decidua and musculature by large syncytial wandering cells and large multinucleated giant cells was noted (*Fig. 5*). Many of these cells were found within venous sinuses. Occasional sheets of syncytial cell masses were found within the areas of hemorrhage and necrosis. Considerable polymorphonuclear infiltration was present. The histologic picture suggested an atypical chorionepithelioma (syncytial cell type). Hysterectomy was advocated and the procedure was undertaken a week after the curettage. At operation the tubes were found greatly thickened. From the fimbriated ends pus exuded freely. Plastic exudate covered the posterior surface of the large boggy uterus, the adnexa and filled the *cul-de-sac*. In face of the peritonitis it was decided to abandon the hysterectomy and only a bilateral salpingo-oophorectomy was performed. Histopathologic report was bilateral acute suppurative salpingitis. There were multiple lutein cysts of the ovaries (up to 3 cm. in size). The patient made an uneventful recovery. The Friedman test (performed eleven and fourteen days after the curettage) with diluted urine (1:10) and with undiluted urine was negative. The patient has been closely followed and Friedman tests have been performed at frequent intervals. These have all been negative and the patient has remained perfectly well.

Careful histologic examination disclosed merely an exaggeration of syncytial cell proliferation which parallels the histologic reports of many of the reported chorionepitheliomas that follow hydatid mole. Frank has said:

"When the histology in the opinion of a skillful pathologist is doubtful, some cases which have been considered chorionepithelioma were probably not malignant, being atypical retained normal trophoblastic elements. The opposite, however, also holds true."

On one occasion he examined uterine curettings and reported "infected abortion." The patient died within the year from typical chorionepitheliomatous metastasis. Mistakes are so readily made, particularly when the pathologist sees only a few sections, that more and more emphasis and reliance should be accorded the biologic tests.

A striking fact connected with this case was the acute infection of the uterus and tubes and the peritonitis. This feature often accompanies this condition and explains the term "syncytial endometritis," readily used to describe it. Meleney[13] reported a case of "syncytioma" that terminated in acute peritonitis. Schmauch pointed out that deaths reported in patients with lesions described as syncytioma were most often due to septicemia and peritonitis rather than progressive metastases.

SYNCYTIAL HYPERPLASIA ACCOMPANYING INVASIVE MOLE

Case 6.—We have recently followed the progress of a young woman* with an invasive mole who had several bouts of hemoptysis. This case is being reported by us in detail elsewhere. Roentgen ray studies of the chest revealed metastatic nodules in the lungs. Following the emptying of the uterus of the molar tissue, the patient continued to bleed. The gonadotropic content of the urine assayed 5,000 m. u. per liter. Hysterectomy was performed and the patient progressively improved. Roentgen ray studies of the lungs at repeated intervals disclosed complete regression of the metastatic nodules by the fifth month following hysterectomy. Three weeks after hysterectomy the gonadotropic content of the urine assayed but 150 m. u. per liter. A recent Friedman test (ten months after operation) was negative.

Histologic examination of sections of the uterus revealed infiltrating villi covered by proliferating layers of Langhans' cells and syncytium. Accompanying these processes was an intensive invasion of the myometrium by syncytial cells. Particularly interesting to note, moreover, were the sections of tissue which on microscopic examination failed to reveal any villi, but showed marked syncytial cell reaction and invasion of venous sinuses (*Fig. 6*) by sheets of syncytial cells. The manner of deportation of syncytial cells by the blood stream and lodgment in the lungs in this case is readily conceivable.

*This patient has been under the care of C. Thompson, of the Millen Hospital, Millen, Georgia, and with whose cooperation the case study has been made possible.

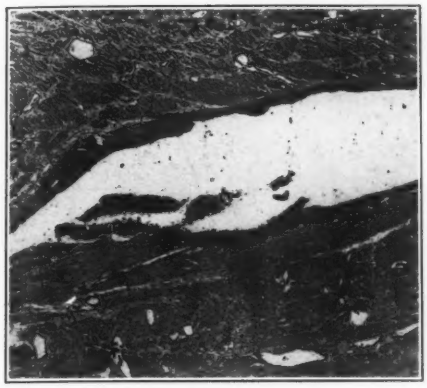

Fig. 6 (Case 6)
Syncytial hyperplasia accompanying invasive mole. Note the nest of syncytial cells lying in the venous sinus. Deportation of cells with lodgment in the lungs occurred in this case.

This is the type of case which is frequently interpreted as chorionepithelioma (chorio-adenoma destruens) with pulmonary metastases in which spontaneous regression occurs. We are inclined to regard such neoplasms as (locally) malignant hydatid moles. Deportations of syncytial masses are not infrequent catastrophes in invasive mole. These frequently lodge in the lungs or vagina and are notoriously known to regress in the majority of instances, particularly after removal of the uterus. It is possible that true chorionepitheliomas may arise from invasive moles.

SUMMARY

We have inquired into the nature of so-called syncytioma by tracing the vagaries of syncytial cell activity as disclosed by histologic study. To illustrate the different phases of the problem, six case reports are presented in which histologic study showed varying degrees of syncytial hyperplasia. The tissues examined were curettements or uterine sections obtained from an interrupted pregnancy, an abortion, a complete abortion, a suspected hydatid mole, a hydatid mole and an invasive mole. Syncytial proliferation and invasion of the uterine musculature in pregnancy, abortion, or hydatid mole may be so marked as to be mistaken easily for chorionepithelioma. The follow-up history and the biologic hormone assays confirmed the benign nature of the proliferative syncytial processes under study. It is felt that the term syncytioma is misleading. Growths composed of syncytium and large numbers of syncytial cells are not syncytiomas, but are chorionepitheliomas. On the other hand, uterine conditions in which there is invasion of the myometrium and blood spaces by syncytial cells in sheets, giant cells or wandering cells are not syncytiomas, but examples of exaggerated syncytial cell reaction to pregnancy, that is, syncytial hyperblastosis.

A proper evalution of histologic criteria and biologic hormone assays will lessen the number of reported chorionepitheliomas and tend to correct the great discrepancies in its incidence. A fuller appreciation of the remarkable extent of the infiltrative qualities and proliferative features of the syncytial cell reaction of pregnancy is urged lest due to our ignorance we needlessly sacrifice many a young woman's generative organs. In conclusion, we leave with you for your contemplation and decision: should the syncytial endometritis or the so-called syncytioma be elevated to the dignity of a malignant neoplasm, a chorionepithelioma?

We wish to express our gratitude and acknowledge the source of our material. The study of numerous histologic sections has permitted us to obtain a more general view of the subject. The following have generously offered us histologic sections, case histories, and so on: Arthur H. Curtis, Chicago, Illinois; Charles Geschickter, Baltimore, Maryland; Adrian W. Voegelin, Philadelphia, Pennsylvania; A. Johnston Buist and Kenneth M. Lynch, Charleston, South Carolina; G. O. Oswalt and I. Milton Wise, Mobile, Alabama; Robert A. Kimbrough, Jr., Philadelphia, Pennsylvania; Otto Saphir and W. Saphir, Chicago, Illinois; C. Culbertson, Chicago, Illinois; Joseph J. Mundell, Washington, District of Columbia; J. Pritchard, Montreal, Canada; L. C. Simard, Montreal, Canada; Leo Spector, Montreal, Canada; K. Terplan and S. Sanes, Buffalo, New York; Cleveland Thompson, Millen, Georgia; R. A. Lyon, Washington, District of Columbia; Henry Brody and David Perla, New York, New York; and T. R. Waugh, Montreal, Canada.

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DISCUSSION (*Abstract*)

Dr. Geo. T. Caldwell, Dallas, Tex.—An unusual fascination has always surrounded the invasions of maternal tissues by fetal ectoderm, and it is true, as the authors suggest, that confusing intra-uterine pathologic processes are produced by hyperplasias and neoplasms of this chorionic epithelium. Certainly trophoblastic hyperplasias with invasion of the underlying myometrium are frequently observed in uteri removed following interrupted pregnancies and with retained placental tissues. Fortunately, most of these hyperplasias are easily differentiated from malignant tumors of the chorionepithelioma type, although I have often wondered what the course of events would have been if the uterus had remained *in situ*.

The infrequency of malignant tumors of chorionic epithelium deserves to be stressed as the authors have seen fit to do. In our last 2,000 autopsies, selected largely because of the interest of the clinician in determining accurately the cause of death, the diagnosis of chorionepithelioma has not been made once; and in 50,000 surgical cases studied pathologically in Baylor University Hospital during the past fifteen years, no malignant tumor of chorionic epithelium has been encountered.

The term syncytioma, as formerly used, is evidently misleading and inaccurate and no longer serves any useful purpose. There is no apparent reason why excessive proliferations of trophoblastic epithelium should not be subdivided into hyperplasias and neoplasms as in other histogenetic groups. And, for clinical purposes, as sharp division as possible should be made between benign and malignant types of growth.

It is disconcerting to admit that chorionic epithelium of relatively benign type may occasionally give implantations in vagina, lung or elsewhere and subsequently undergo retrogression, but a somewhat comparable behavior on the part of endometrium is now fully recognized following the interruption of its hormone stimulation.

With more accurate morphologic diagnoses and the discreet use of quantitative biologic tests, the conservative management of all those conditions with associated trophoblastic hyperplasias seems indicated in the light of the infrequency of malignant transformation of such hyperplasias.

THE ROENTGEN DIAGNOSIS AND TREATMENT OF BENIGN GIANT CELL TUMOR OF BONE*

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The term "benign giant cell tumor" is here used to apply to those slow growing, multicystic lesions usually involving the ends of long bones. They sometimes occur in flat bones. They arise in bones of cartilaginous origin.[6] A majority are found about the knee joint, that is, in the distal end of the femur and the proximal end of the tibia and fibula. In this series there are: 2 in the proximal end of the femur, 2 in the distal end of the femur, 3 in the proximal end of the tibia, 1 in the distal end of the tibia, 1 in the distal end of the radius, 1 in the proximal end of the humerus, 2 in the pelvis and 1 in the mandible. They most frequently occur in persons between 20 and 30 years of age, but are found earlier and later. Our youngest patient was 7 years old, the oldest over 40. The latter was seen in a Negro man, who stated that the growth had been present ten years.

Radiographically we have found two types of giant cell tumor. One (*Fig. 1*) may be termed the trabeculated type. This, in our experience, is the more common type; it is the variety most often described. They are usually seen at or near the end of a long bone. The transition from normal bone is abrupt. The diameter of the bone is increased. The involved bone becomes club-shaped. The cortex of the expanded bone becomes quite thin, but remains intact, if there has been no fracture. No periosteal thickening or elevation is seen at the point of invasion. A network of varying density (trabeculation) traverses the lesion in all directions, dividing it into multiple sections.

The second (*Fig. 2*) variety we have encountered presents a homogenous swelling at the end of a long bone, the density being approximately that of the surrounding soft tissues. As in the trabeculated type, there is no periosteal reaction at the site of invasion. There is usually a ragged projection from the normal bone at this level. Few, if any, trabeculations are seen. Those oc-

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Fig. 1
Trabeculated type giant cell tumor of bone. The cortex is expanded, but remains intact. The cross striation (trabeculation) is clearly seen.

casionally seen are so thin as to be barely discernible. Because of the complete solution of the involved bone, it is difficult, or impossible, to detect any remaining cortical bone. Kirklin and Moore[8] refer to this as the "lysis" type of giant cell tumor.

It is not always possible to determine roentgenographically whether a trabeculated, destructive lesion involving the end of a long bone is a giant cell tumor or a solitary bone cyst. If one adheres to the dictum that the giant cell tumor involves the epiphysis, certain destructive lesions which involve the metaphysis, stopping abruptly at the epiphyseal line, and leaving the epiphysis intact must be classed as bone cysts. Yet, on the x-ray film, they present the characteristic appearance of giant cell tumor. Pierce,[12] in discussing this matter of involvement of the epiphyses, noted this. He observed that wherever the epiphyseal discs are still present, the neoplasm has not invaded the disc, being apparently restricted to the end of the diaphysis, the metaphysis, but that wherever the epiphyseal disc has been obliterated by maturity of the bone the tumor proceeds throughout the cancellous structure to the under surface of the articulating cartilage plate. If one observes the stroma in each of these lesions, little difference is seen. As was pointed out by Nelaton,[11] it is the presence of the foreign body giant cells that makes the diagnosis. Histologically, it would appear that the solitary cyst and the giant cell tumor are but different stages of the same disease. Osteitis fibrosa cystica presents the same lesion involving many bones. In recent years the relationship between parathyroid disease and fibrocystic disease of bone has been frequently mentioned. More recently, Murphy[10] has reported a typical giant cell tumor which failed to respond to the usual local radiation therapy, but calcified rapidly following radiation of the parathyroid area.

Chondromas may assume an appearance closely simulating giant cell tumors, but they are rarely found in long bones. Usually they involve the small bones of the hands and feet. When they do occur in long bones, the lobulations are usually smaller, their wall appearing thicker. The solitary bone abscess (Brodie's abscess) causes central destruction, but there is an associated osteitis and periostitis. The expanded bone is due to bone production and is a dense structure.

Osteolytic osteogenic sarcoma and metastatic bone lesions simulate the lysis type of giant cell tumor more than the trabeculated type. Both of these, being malignant destructive lesions, cause no expansion of the cortex. In the osteolytic type there is usually a perceptible reaction in the periosteum at the point of invasion. This is absent in the giant cell tumor. Metastatic lesions occur at or near the entrance of the nutrient artery.

TREATMENT

The benign nature of the giant cell tumor of bone was emphasized by Nelaton[11] as early as 1863. In 1879, Gross,[7] of Philadelphia, showed the relatively favorable prognosis of the central giant cell type of bone tumor, but recommended amputation of the involved limb, except in cases in which the tumor could be completely resected. Until 1910 it was customary to amputate a limb when this lesion was diagnosed. At this time Bloodgood[1] again emphasized the benign character of this lesion and in 1919 reported 47 cases treated by curettage without recurrence.

Fig. 2
Non-trabeculated (lysis) type giant cell tumor of bone. The cortex is more clearly seen than is frequently the case. No cross striation (trabeculation) is seen.

Pfahler[13] was the first to treat this lesion with the roentgen ray. His first case was treated in 1906 and reported in 1907. Since then many others have reported favorable results following the treatment of this lesion with x-ray. It has been our experience that the trabeculated type responds well to this type of therapy. Our experience with the lysis type has not been satisfactory.

We have used no fixed technic in treating these cases. The voltage used has varied from 145 to 200 k.v. The filtration has varied from one-half to one millimeter of copper. The number of treatments and the amount given has depended upon the appearance of the lesion as demonstrated by repeated x-ray examinations. If progressive calcification was observed in the lesion, we continued sub-erythema doses at four, five or six week intervals. If, on the other hand, new areas of destruction appeared, heavier dosage was given. Deep seated lesions were, of course, given heavier radiation than those near the surface. As some of the lesions were at or near the epiphyseal line, the growing portion of the bone was necessarily treated. No attempt was made to shield this area. As yet we have not encountered any disturbance in the growth of the bone following radiation.

Fractures are frequent in giant cell tumors. It has been our experience that the true nature of the lesion is rarely determined until there has been an injury and an x-ray examination is made to determine the presence or absence of fracture. Naturally these receive supportive treatment in addition to the x-ray treatment. However, if a giant cell tumor is discovered in which no fracture has occurred, the part should receive supportive treatment if fracture is likely to occur. This is particularly true in the weight bearing bones, such as the femur, the tibia, the vertebrae and the acetabulum. Deformity is the penalty for overlooking this detail.

CASE REPORTS

Case 1.—E. H., a white woman, aged 23, a school teacher, was first seen in July, 1926. Several months previously she fell, injuring her left knee. As the knee continued to ache, she consulted her local physician. He treated her for "rheumatism." No x-ray examination was made. As the knee did not improve, she consulted an orthopedic surgeon. He referred her to us for x-ray examination, which revealed a destructive lesion involving the proximal end of the left tibia, diagnosed giant cell tumor. It was handled surgically. One year later, as the knee had again swollen, another x-ray examination was made and the lesion had recurred. She was again operated upon. About a year later x-ray examination showed recurrence. She was referred to us for x-ray treatment. The growth was in intimate contact with the joint cartilage and the surgeon decided against further operative interference. Using 180 k.v., 50 cm. distance, 0.75 mm. copper and 1.0 mm. aluminum, 240* r were given over the knee anteriorly and 240 r posteriorly in four days in July, 1928. Subsequent treatments given were with 170 k.v. and 0.5 mm. copper. In September she received 315* r, in October 315* r, in November 255* r, in December 255* r, in January, 1929, 255* r, and in March 85* r. No further treatment has been given. She has continued to teach. The knee is not painful, but is limited in motion to about 15°. A rather deep scar persists.

Case 2.—J. D., a white boy, aged 12, a student, was first seen in February, 1932. He had sprained his right wrist eighteen months previously. The wrist became swollen, but subsided to almost normal. About three

months later, a cow kicked him on the same wrist while he was milking. The wrist swelled again. With supportive treatment and rest, the swelling subsided. Three or four months later he fell, again injuring the right wrist. The wrist swelled again and has remained enlarged since. Swelling was quite obvious on physical examination. X-ray examination revealed a destructive lesion involving the distal end of the shaft of the radius, stopping abruptly at the epiphyseal line. We considered it a giant cell tumor. With 170 k.v., 50 cm. distance, 0.5 mm. copper and 0.1 mm. aluminum the following treatment was given: February, 210* r anteriorly and 210* r posteriorly. March, April, May, June and September the above dose was repeated. In October, 140* r were given anteriorly and posteriorly.

This boy has been seen frequently since the last treatment. He uses his hand easily. There has been no recurrence.

Case 3.—W. H., a white boy, aged 7, was first seen at the Hillman Clinic October 10, 1933. Two days previously the patient fell off the steps and injured the left shoulder. X-ray examination October 11, 1933, showed "Comminuted fracture just below the head of the left humerus with impaction." May 2, 1934, the patient was first seen by one of us (Meadows). X-ray examination showed: "Fragments in good position. Marked evidence of giant cell sarcoma." X-ray treatment was begun June 1, 1934, using 145 k.v., 0.5 mm. copper, 1.0 mm. aluminum, 15-inch distance, 180 r over the right shoulder anteriorly and posteriorly. July 5, 1934, the same dosage was repeated, and again August 9 and 10. October 18 and 19 270 r were given over the shoulder anteriorly and posteriorly. December 17 and 18 as above. April 2 and 4, 1935, 180 r were given over the shoulder. This was repeated May 7 and 8. The lesion showed progressive calcification.

Case 4.—I. B., a colored boy, aged 18, a farm hand, was first seen in August, 1934. For some months he had complained of pain in the left side of the lower jaw. A tooth (left lower, first bicuspid) was pulled without relief. Following the extraction the jaw swelled. On physical examination the tumefaction of the left half of the mandible was obvious. X-ray examination revealed a destructive lesion which was diagnosed giant cell tumor. Using 190 k.v., 50 cm. distance, 0.75 mm. copper and 1.0 mm. aluminum, he was given the following treatment: in August, 1934, 540* r in four days over the left half of the mandible and 180* r over the right. This was repeated in September and November. In December he was given approximately 500* r over the left lower jaw over a period of three days.

The pain and discomfort were relieved. In 1936 we received a letter saying that he felt well, but that at times there was a discharge. He has not returned for further treatment.

Case 5.—S. N. D., a white woman, aged 19, a telephone operator, was first seen in March, 1931. In April, 1930, she noticed that the right ankle was swollen and ached. She went to a chiropractor. As the ankle became steadily worse, she consulted a physician, who referred her to an orthopedic surgeon, who referred her to us for x-ray examination. This revealed a destructive lesion involving the distal end of the tibia. The appearance suggested giant cell tumor. It was treated surgically. The tissue was submitted to the pathologist, who diagnosed it "giant cell sarcoma," but added the following comment:

"The foundation tissue of the tumor is composed of cells that are proliferating more rapidly than is usual in the benign giant cell tumor. The tumor is potentially malignant."

This was March 2, 1931. X-ray treatments were advised and between March 24 and 28 she received 410* r over the ankle and 90* r over the right groin, using 190 k.v. and 0.5 mm. copper. Further treatment over each area was planned, but the patient did not return. However, on February 1, 1932, she came for x-ray examination of the ankle again, as the pain had returned. This revealed extension of the tumor and she was again operated upon. The pathologist reported:

"There is still the suggestion of potential, if not actual, malignancy."

Further x-ray treatment was advised and given. She received 960* r in four days in May, June and July; 720* r in September and October of 1932. At this time x-ray examination revealed considerable calcification at the site of the tumor. On January 17, 1933, she was readmitted to the hospital, giving a history of having had a fall, which produced severe pain in the right hip. X-ray examination revealed a destructive lesion involving the right acetabulum and horizontal ramus of the pubis with a fracture through the acetabulum. She was kept on a Bradford frame until she was sufficiently comfortable to come to the office for treatment. X-ray treatment over the hip was started in April, 1933. Over a period of six days she received 480* r over the hip anteriorly and 240* r posteriorly. This was repeated in July. The lesion showed considerable calcification and treatments were discontinued. In September, 1934, she complained of pain in the right knee. X-ray examination revealed a giant cell tumor involving the proximal end of the tibia. She was given 560* r over this lesion in four days in October, 1,320* r in nine days in November. She apparently improved until she again fell in December, sustaining a fracture through the tumor in the tibia. In March, 1935, she received 840* r over the knee and in April 960* r. The lesion showed evidence of recalcification and treatments were discontinued. She returned in February, 1936, because of return of pain in her knee. Destruction had again occurred and she was given 1,200 r in six days, using 200 k.v. and 1.0 copper. The following month, because of discomfort in the right hip, she was given 1,000 r over this area. She did not return for further treatment. The knee continued to enlarge and was very painful. The leg was amputated December 28, 1936. The microscopic diagnosis was: "Malignant giant cell tumor of bone," and the comment was made: "In part, the tumor still preserves the giant cell character of the benign tumor, but in others it is a frank fibrosarcoma. It is purely osteolytic." The patient died March 15, 1937, of lung metastasis.

Case 6.—V. B. B., a white man, aged 31, was first seen in June, 1934. Two years previously he fell, hurting his right knee. Since then he has had "rheumatism" at times. The knee swells and aches. At times he cannot walk because of the pain. The knee has gradually gotten worse. X-ray examination revealed a giant cell tumor at the proximal end of the right tibia. Using 190 k.v. and 0.5 mm. copper, he received 840* r in seven days in June, 1934, the same in July, 720* r in Au-

*Dosage computed as we had no r-meter at this time, nor were we using the same machine.

gust and in October. At this time recalcification was evident in the tumor and treatment was stopped. Because of recurrence of pain and evidence of new areas of destruction he was given 1,556 r in June, 1936, and 1,188 r in July, using 200 k.v. and 1.0 mm. copper. In January, 1937, he was given 1,584 r because of return of symptoms. At the present time he is apparently well.

Case 7.—M. M., a white man, aged 24, fell on June 3, 1935. The left hip was broken. He was referred to us on September 24, 1935. X-ray examination at this time showed a fracture through a destructive lesion involving the trochanters and neck of the left femur. The appearance was that of giant cell tumor. Using 200 k.v., 50 cm. distance, 1.0 mm. copper and aluminum, he was given 1,580 r between September 24 and October 3, and 1,600 r between November 13 and 20, 1935. In February, 1936, he was given another 1,600 r. An x-ray film made at this time showed continued increase in calcification. He did not return for further treatment.

Case 8.—V. B., a white woman, aged 22, was admitted to the hospital December 6, 1935, with a fracture of the distal end of the left femur. One year previously, while playing basket ball, she fell, hurting her left knee. One week previously, she again fell, hurting the same knee. The pain was intense, and she could not bear any weight on the left leg. X-ray examination revealed a fracture into a destructive lesion involving the condyles of the femur. It was diagnosed giant cell tumor. A cast was applied. Treatments for the first month were given through the cast. Using 200 k.v. and 1.0 mm. copper and aluminum, she was given 1,200 r in six days in December, 1935, January, March, May and June, in 1936. The last x-ray showed considerable calcification. She has remained well.

Case 9.—Mrs. W. M., a white woman, aged 42, was first seen in May, 1936. She had had pain in the right hip for about one year. For the past two or three months the hip had been very painful. X-ray examination revealed a destructive lesion involving the ischium on the right side and extending upward to involve the acetabulum laterally and the descending ramus of the pubic portion medially. Using 200 k.v., 50 cm. distance, 1 mm. copper and aluminum, treating through anterior and posterior portals, we administered 1,738 r between May 21 and June 4, 1936; 2,178 r between July 13 and 25; 2,178 r between August 31 and September 11 (594 r of this amount was given laterally); 1,584 r between October 21 and October 29; between October 30 and November 3 she received 792 r laterally; between December 28, 1936, and January 9, 1937, she received 792 r anteriorly, posteriorly and laterally; between February 22 and March 6, she received 792 r anteriorly, posteriorly and laterally; between April 19 and 23, she received 990 r laterally, and between April 26 and May 4, she received 792 r anteriorly and posteriorly. No further treatment has been given. This patient has remained in bed the last several months because of pain. At times the films showed evidence of increase in calcification. However, in a short while this disappeared. The films made this year show no calcification. There has been little or no change in the appearance of the lesion; there was no metastasis to the lung when we saw her last. Her physician states that she now has no cough. Her chief complaint is pain.

The next two cases are considered separately, as one is a spontaneous healing. The other probably did not receive enough x-ray treatment to have any effect on the lesion.

Case 10.—A colored man, aged 40 years plus, a laborer, stated that he had had "a swelling" in the knee for about ten years. X-ray examination shows considerable expansion at the distal end of the femur. Multiple locules with thick walls were seen. The appearance suggested healed giant cell tumor.

Case 11.—W. K., a white farmer, aged 28, had had an aching pain in the left hip for about a year. A few months previously his hip was x-rayed and reported negative. Because of continued pain his family physician brought him to us. On the trip to town, their car was run off the road by a truck. The patient fell from the seat of the car to the floor, which caused severe pain in the left hip. X-ray examination revealed a giant cell tumor involving the trochanters and neck of the left femur with fracture into the lesion. He was treated the same day, May 13, 1936, and the following day. He was given 200 r over the hip anteriorly each time, a total of 400 r, using 200 k.v., 50 cm. distance, 1 mm. copper and aluminum filter. No further treatment was given, as he did not return.

His physician reported to us in November that he is free of pain. He made his crop this year.

SUMMARY

We have shown two types of giant cell tumor, distinguishable roentgenologically, the trabeculated type and the non-trabeculated or lysis type. We believe the trabeculated type ordinarily responds well to radiation therapy. There is some doubt as to the advisability of depending on radiation alone in treating the non-trabeculated type if proper surgical procedure can be carried out. The last two cases reported suggest that some giant cell tumors heal, or become arrested, spontaneously.

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DISCUSSION (*Abstract*)

Dr. Vincent W. Archer, Charlottesville, Va.—The subject has been covered well, but there are some points which I wish to emphasize: first, the difficulty of diagnosis. Many of these lesions are somewhat atypical, and may be mixed in character, and the combined efforts of the microscopist, the surgeon, and the radiologist must be exerted. One of our series exemplifies this point. A woman, aged 30, with pain in the hip, was examined radiologically in 1927. In the trochanteric region and involving the neck and head of the femur there was a typical trabeculated giant cell tumor, but in the shaft, at the lower margin of the lesion, there was a moth-eaten erosion, not sharply defined. A diagnosis of benign giant cell tumor with malignant change was ventured, although at that time no such case was in the literature, and the late Dr. Bloodgood had made the statement that no benign giant cell tumor ever became malignant. A biopsy was done on the trochanteric region, the report being "benign giant cell tumor." I insisted that, in spite of the biopsy, the lesion looked malignant, and the surgeon was persuaded to do a hip disarticulation. Sections from the lower part of the lesion showed malignant degeneration, and the patient died three years later of metastases. Pain is an almost invariable accompaniment of bone malignancy and is fairly uniformly absent in benign giant cell tumor unless there is a fracture. This patient also brings out the fact that the site of biopsy should be guided by the radiological findings, the most malignant portion of the lesion being sectioned. The further point is emphasized that one biopsy reported as benign should not be taken as final in the face of other fairly definite evidence.

The benign character of these lesions may alter, even years after apparent cure or arrest. A girl of 17 years with a painful swollen knee was examined in 1925. X-ray showed a typical benign giant cell tumor of the upper end of the tibia with pathological fracture. X-ray therapy was instituted and she was given several treatments of approximately 250 r each over a period of two years. The condition was apparently cured, but it was thought best to examine the patient every six months. Finally in 1934, nine years after the onset, an osteolytic process was seen. Again, as in the previously cited case, pain was a prominent feature after malignant changes had set in. Beware of pain in these cases either initially or after treatment. This was treated with radiation with no response, so a tourniquet biopsy was performed which showed a quite malignant fibrosarcoma. The leg was amputated above the tourniquet and at present, about three years later, there has been no evidence of return.

In talking with a good many radiologists and surgeons dealing with large numbers of malignant tumors, it seemed to be the fairly general opinion that benign giant cell tumor of the upper end of the tibia was quite prone to become malignant, whether left alone or treated either surgically or radiologically. Personally, I wonder whether to treat the tumors in the upper end of the tibia or to advise amputation. Most certainly they should be examined at frequent intervals.

REGIONAL ILEITIS*

CLINICAL REPORT OF TWO CASES

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Nonspecific inflammatory disease of various portions of the intestinal tract has been known for many years. A review of the literature reveals considerable recent interest in this condition described under various terms such as "nonspecific granuloma," "infectious granuloma," "benign granuloma," and "inflammatory tumor of the intestines," which, while resembling new formations, are neither neoplastic nor due to any specific organism.

The revival of interest in these conditions was stimulated when Crohn[1] and his associates in 1932 presented for consideration a definite clinical and patholoical entity which they called "regional ileitis." Their report was based on a study of thirteen resected specimens. The lesion described involved the ileum (25 to 35 cm.) and ended abruptly at the ileocecal valve. This segment is greatly thickened, heavy and reddened. The lumen of the bowel is irregularly distorted and narrowed. The mucosa is subject to a destructive, ulcerative process with edema presenting a bulbous appearance (*Figure 1*). The submucosal and muscular layers show inflammatory, hyperplastic and exudative changes. The mesentery of the involved segment is stiff, thickened, and contains enlarged lymph nodes. Adhesions of the involved bowel to the neighboring viscera with slow perforation and formation of fistulous tracts was a characteristic feature.

The subsequent rapidly growing literature on this subject attests the importance of Crohn's contribution. Some of the papers[2,3] deal with the subject at great length. Others are only clinical reports of a few cases with comments. Such tumor-like processes are reported as being found in any part of both the large and small intestine. Judging from many reports, the disease thus seems to be a clinical and not a pathological entity, the lesions of which may occur at various points in both the small and large intestine.[4,5,6,7]

The clinical features vary according to the

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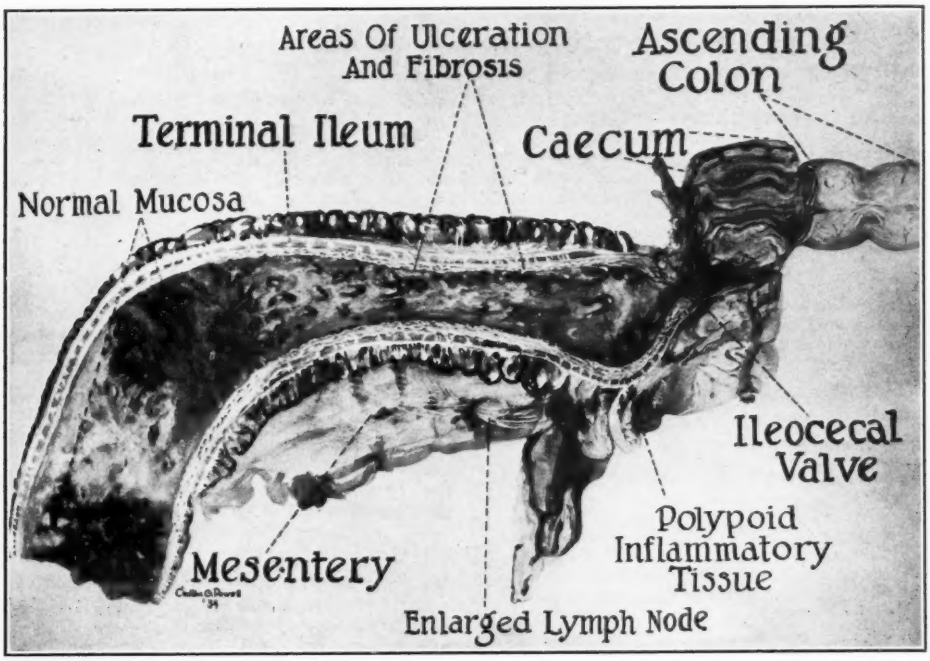

Fig. 1

Artist's drawing of resected specimen in Case 1 showing greatly thickened terminal ileum with destructive ulcerative lesions and polypoid inflammatory changes with bulbous appearance.

extent and duration of the disease. Crohn has grouped cases into four types, as follows: (1) those with symptoms simulating acute appendicitis, with the presence of a palpable mass in the right lower quadrant; (2) symptoms of ulcerative enteritis; (3) symptoms of chronic obstruction of the small intestine; (4) persistent and intractable fistulae in the right lower quadrant, following previous drainage for abdominal abscess.

Since the inflammatory process is a progressive one, the clinical picture varies with the duration of the disease as well as the specific area involved. Diagnoses thus far have been usually established by pathological study of the resected specimen. Indeed, the symptoms are so variable that it is doubtful that they can be assembled into a well-fitting clinical syndrome. With greater care in history taking, improved roentgenologic technic and surgical exploration greater alertness in recognizing the disease should develop.

This condition is more common in the earlier decades of life, after the first, and is more common in males than females. However, our two cases were both females, ages 20 and 50 years. The main symptoms are first, fever, although fever can be absent; diarrhea is often prominent, but without tenesmus; loss of weight and progressive anemia are noted. The stools sometimes are mushy or liquid and contain free pus, coagulated lumps of mucous and streaks of blood. When the lumen becomes unduly contracted, constipation and symptoms of obstruction appear. Vomiting may occur at times with severe abdominal cramps. Pain is a prominent symptom and since the lesion is usually near the ileocecal region, tenderness may be present at this point. Bargen[8] says that with this type of history and typical x-ray deformity they now usually diagnose the condition preoperatively at the Mayo Clinic, although this condition was rarely diagnosed until the recent revival of interest.

Roentgenologic investigation is a most essential feature in establishing a diagnosis. Kantor[9] summarizes his technic and findings as follows:

The usual opaque meal is employed as well

as a barium enema. Serial observations are made at hourly intervals from the period just before the cecum fills to the normal period of emptying. This is about three to nine hours after the ingestion of the opaque meal.

The abnormalities observed may be either in the ileum or the colon or both. The changes in the latter may be reflex in nature. The principal changes in the ileum are: (1) filling defects just proximal to the cecum; (2) abnormality in contour of the terminal loop of the ileum; (3) a dilatation of the loops just proximal to the lesion. Kantor describes a roentgenologic sign which, though not pathognomonic of the disease, is characteristic. He called this the "string sign," a thin, slightly irregular linear shadow suggesting a cotton string in appearance and extending from the last visualized loop of ileum through the entire extent of the filling defect and ending at the eliocecal valve. It represents the attenuated barium filling of the greatly contracted intestinal lumen. Weber's[6] description is that of a "twisted cord" appearance. In our first case we obtained this appearance by a barium clysma, which was well visualized under the fluoroscope and in the film (*Fig. 2*). The absence of the "twisted cord," however, should not exclude the disease, as it might be present in other conditions and absent in certain stages of regional ileitis.[10]

Fig. 2
Roentgenogram obtained by barium enema showing typical beaded string appearance of terminal ileum (Case 1).

The following case reports represent entirely different clinical varieties and stages of this interesting condition.

Mrs. C. F., aged 20 years, became ill with pain in the right lower quadrant of the abdomen which was associated with nausea, but no vomiting. The past history was of no consequence except for an attack of typhoid fever five years previously. She had been quite well in the interim.

The temperature was 99°. Physical examination showed a scaphoid type of abdomen with moderate tenderness over the region of the appendix, and the presence of an indefinite mass in this area. All other findings were essentially negative. The white blood count was 18,500 with 69 per cent polymorphonuclear leukocytes. The abdomen was explored surgically, through a right rectus incision, for supposed acute appendicitis. A small amount of pearly gray peritoneal fluid was present. The appendix was found to be normal in appearance. The terminal five inches of the ileum showed signs of acute inflammation with a sharp line of demarcation between diseased and healthy tissue. The mesentery was greatly thickened and contained many enlarged lymph nodes, several of which were as large as the end of the index finger. The inflamed area of the ileum was "beefy" red in color, the walls were markedly indurated, which caused a great increase in the diameter. There was apparently marked stricture of the lumen. No intra-abdominal adhesions were found. Resection of the terminal ileum was indicated, but it seemed advisable to postpone this procedure to a later date, when the patient had been properly prepared by catharsis and enemata. The appendix was removed and also one of the enlarged regional lymph nodes for microscopic study. Convalescence was marked by an irregular slight rise in evening temperature, which reached 101° on the ninth day. At this time the patient had nausea and some pain in the lower right abdominal quadrant. There was no wound infection, and she was dismissed from the hospital on the eleventh day.

About one month later she returned for the second operation. During this time she had continued to experience soreness in the lower abdomen, some nausea and occasional attacks of cramping. On several occasions she had mild diarrhea.

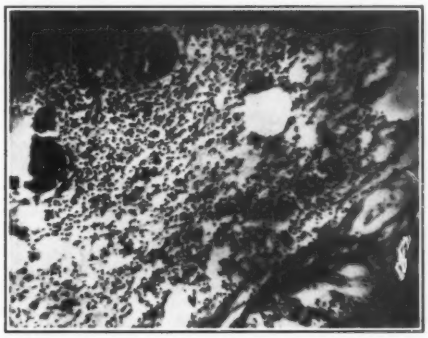

Fig. 3
Microphotograph of section taken from the wall of the ileum showing chronic inflammatory reaction, increased fibrous tissue, and collections of small round cells and plasma cells.

Upon exploration the condition was found to be essentially the same as previously, except that the inflammatory process extended several inches higher and the omentum was adherent to this part of the ileum. The terminal eleven inches of the ileum, together with its mesentery, the cecum and about one-fourth of the ascending colon were resected. The ends of the bowel were closed and a side-to-side anastomosis was done between the ileum and end of the remaining part of the ascending colon. Convalescence was uneventful and she was dismissed from the hospital on the thirteenth day.

Two years have elapsed since this operation. She has continued quite well and has gained twenty-four pounds in weight.

The second patient, Mrs. B. C., 50 years of age, is the mother of 14 children. She passed the menopause five years previously and denies any serious illness prior to the present trouble. Five or six months previously she began to tire easily and complained of poor appetite and vague abdominal distress. Her trouble continued to grow worse until spells of colicky pain in the region of the umbilicus developed and there were spells of nausea and vomiting. She tended toward constipation and had to rely on cathartics for relief. About a week before entering the hospital, she discovered a hard tender mass in the right iliac region.

On entrance to the hospital her temperature was normal, 98.2°. She was pale and emaciated. Blood pressure was systolic 120 and diastolic 70. The urine contained a trace of albumin and a few pus cells. Her hemoglobin was 67 per cent, red cell count 3,780,000, white cell count 8,200 with 67 per cent polymorphonuclear leukocytes. Examination of the feces and x-ray of the colon were not done.

The physical findings were of no importance except for the essential pathologic condition in the right lower quadrant. Bimanual pelvic examination revealed the presence of a hard nodular tender mass about the size of a small grape fruit, which gave the impression of being adherent to the uterus laterally. It was immobile and thought to involve the ovary. A diagnosis of probable ovarian carcinoma was made and laparotomy decided upon.

On February 16, 1937, under ethylene ether anesthesia a low midline incision was made. The tumor mass was easily separated from the right adnexa and found to involve the cecum and terminal ileum. The cecum was lateral with folds of the ileum below, the harder and more nodular portion of the tumor mass seeming to be included in their angle. The ileocecal coil, including the tumor, was mobilized without difficulty. The cecum and about eight inches of the ileum were resected with a triangular portion of mesentery, including all palpable lymph nodes (*Fig. 4*). The ends were closed and a lateral anastomosis made between ascending colon and ileum. The parts were well approximated without tension, affording an ample stoma. Closure was performed without drainage and without ileostomy. Postoperative diagnosis was cancer of the cecum.

Convalescence was not unusually difficult and no complications of interest developed. She was discharged from the hospital on the twenty-sixth day, able to be up and about.

Pathologist's Description (by Dr. I. M. Wise).—The specimen consists of the cecum and about eight inches of the ileum adherent to a tumor mass. The ileum is easily separated. Its walls are somewhat thickened and stiff, but it is otherwise unchanged. The medial wall of the cecum contains a tumor about 4x4x6 cm. which is external to the mucosa. There is no ulceration or other involvement of the mucosa. Sectioned surfaces of the tumor are hard and greyish in color with many small fatty areas in its substance. There are several enlarged lymph nodes in the attached mesentery.

Microscopically, sections of the cecum show the mucosa to be normal and regular with no ulceration. In the submucosa is an extensive infiltration of small round cells and plasma cells (*Fig. 5*). The muscularis is many times thicker than normal, and there is apparently a fibrous tissue replacement around the vessels. Occurring in many scattered groups are collections of round cells and plasma cells. Sections of lymph nodes show no evidence of metastatic deposit, but only that of a hyperplastic lymphadenitis. The diagnosis is nonspeific infectious granuloma, regional ileitis.

DISCUSSION

Laparotomy was performed in both of these cases under mistaken diagnoses of acute appendicitis and cancer of the ovary respectively. This is not surprising when a perusal of the literature reveals the various conditions that must be differentiated, as follows: tuberculosis, appendicitis, disease of Meckel's diverticulum, carcinoma, sarcoma, actinomycosis, Hodgkin's disease, cholecystitis and ulcerative colitis.[11] A group of conditions is thus presented which is most difficult to the general surgeon whose commonest laparotomy is occasioned by acute appendicitis. To the general surgeon outside of the large clinic and teaching centers the gross pathologic diagnosis at laparotomy will usually be that of malignancy or tuberculosis and should prompt him to perform resection if possible.

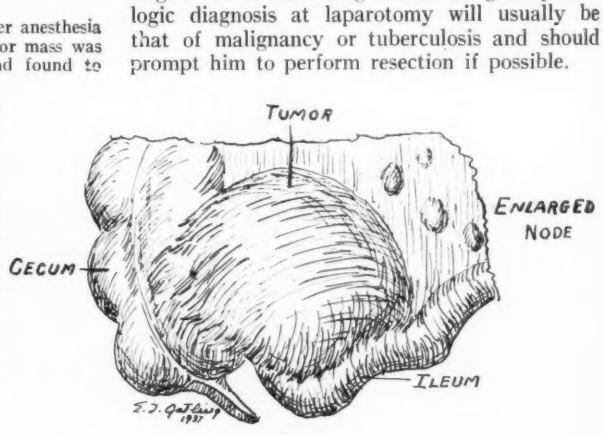

Fig. 4
Diagrammatic representation of resected specimen in Case 2. Tumor mass springing from cecum, with ileum adherent.

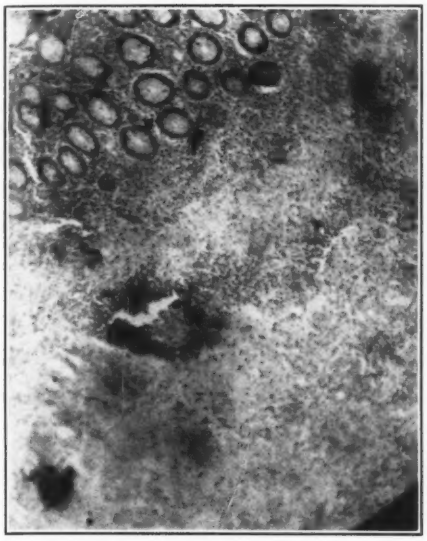

Fig. 5

Microphotograph of section from tumor mass showing chronic inflammatory process. Marked thickening of submucosa with fibrosis and collections of lymphocytes and plasma cells.

A great deal remains to be learned of this condition in many respects.[12] [13] The prognosis as to life, and the incidence of recurrence after radical surgical intervention remain to be established. The end results in cases of the early stages noted at laparotomy in which no surgical intervention is done, would be interesting to know. Criteria for clinical diagnosis should be more accurately established. Once established, do spontaneous cures occur and is there any medical regimen that is of value?

All these features are largely problems to be solved by the large clinics and teaching centers. Meanwhile the general surgeon in the small private hospital must attempt surgical removal according to his technical ability, and interpretation of the gross pathologic condition at laparotomy.

CONCLUSIONS

(1) Two cases of nonspecific granulomata of the intestines are presented in both of which resection of the ileocecal coil was performed with complete recovery. Both are well up to the present.

(2) The first of these cases simulated acute appendicitis and fits very well Crohn's description of regional ileitis. The second simulated malignancy with the pathologic examination fitting that of the combined form of ileocolitis.

(3) Much more work remains to be done to clarify many features of this disease, in all major aspects: etiology, diagnosis, prognosis, and therapy. Meanwhile surgical removal of the lesion seems to be the method of choice.

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DISCUSSION (*Abstract*)

Dr. Ambrose H. Storck, New Orleans, La.—Regional enteritis or segmental enteritis is a term which describes better than does regional ileitis the type of lesion which Drs. Meeker and Frazer have considered in their presentation, for this disease may involve either the jejunum or the ileum as well as the cecum or other parts of the large intestine. Although the etiology of regional enteritis has not been established, the correlation of its various clinical manifestations with operative and autopsy findings has greatly advanced our knowledge concerning this granulomatous process.

At least two types or stages of regional enteritis must be recognized, because for each the diagnostic features and the therapeutic indications are entirely different. There is an early or acute type or stage of regional enteritis which is difficult to recognize preoperatively because of its close simulation of acute appendicitis or acute intestinal obstruction. During this phase, which constitutes an acute lymphangiitis of the intestine with an associated acute mesenteric lymphadenitis, complete involution or restitution of the diseased segment of intestine may be expected, and from personal observations I am in accord with those who believe that regional enteritis encountered during this early or acute stage should be treated conservatively rather than by unnecessary resection of the involved bowel and adjacent mesentery. Then there is a late or chronic type of regional enteritis which follows when involution does not occur after the acute stage; in this type there is a history of long-standing abdominal pain and other symptoms, a mass can usually be felt in the ab-

domen, and external intestinal fistulas may be present. Although the late stage of regional enteritis may simulate intra-abdominal malignancy or hyperplastic tuberculosis, the correct diagnosis is now often made preoperatively. When regional enteritis has progressed to the chronic stage, complete resection of the entire involved intestine is usually necessary. Before beginning such a resection, the entire intestine should be examined so that all "skip" areas can be included in the excision, along with the adjacent mesentery in which enlarged lymph nodes are present or between the leaves of which abscess formation may have occurred.

Under almost no circumstances should enterostomy be done in cases of regional enteritis, since such a procedure is likely to be followed by the formation of an intestinal fistula. Although operations less radical than complete resection, for example, ileocolostomy or terminal ileostomy, often result in temporary relief of the chronic manifestations of regional enteritis, such procedures are usually followed by persistence of recurrence of the granulomatous lesions of the intestine and mesentery.

Dr. Russell B. Bailey, Wheeling, W. Va.—The pathological picture presented by this entity has stimulated a great amount of interest. I should like to add to this discussion the reports of two unusual cases in which the pathological changes were strikingly similar to those described in the ileum except that they were limited to the cecum and ascending colon.

A girl, 23 years of age, had symptoms suggestive of a partial intestinal obstruction, with a palpable tumor mass.

At operation, a tumor involving the cecum and ascending colon was found. There were large lymph nodes in the mesentery of the ascending colon. An ileocolostomy was done, uniting the terminal ileum to the transverse colon. Fifteen days later the right half of the colon and the distal end of the ileum were removed. At the second operation it was found that the tumor had increased in size, being approximately one-third larger. On pathologic examination, the appearance suggested a combination of malignancy and ulcerative changes.

Microscopically, the diagnosis was acute and chronic ulcerative colitis (limited to the cecum).

The second patient, also a young woman, had a large palpable tumor in the right side of the abdomen, which x-ray revealed to be an infiltrating tumor of the cecum and ascending colon.

An ileocolostomy was done, joining the terminal ileum to the transverse colon. Fifteen days later the abdomen was reopened and, to my surprise, the tumor had receded in size until there was only a small nodule, which was very hard, movable, and situated in the ascending colon. The right half of the colon was removed.

The diagnosis, after microscopic examination, was ulcerative colitis.

These two cases, at the first operation, presented almost exactly the same pathologic picture, except that the first one was definitely more acute, as manifested by the greatly enlarged lymph nodes and congestion of the surrounding visceral peritoneum. Both patients had been operated upon previously, the first one for an alleged acute appendicitis six months prior to my seeing her. The other case had had a cholecystectomy twenty-eight months prior to my seeing her.

The findings at second operation in these two cases raise the point of therapy. Should one do an ileocolostomy and then wait for a period of time before considering the removal of the right half of the colon? That would be the most conservative method of handling it. On the other hand, as demonstrated in the first case, perforation, with its sequelae, might be expected.

Both patients are doing well at the present time. The first case feels better and is not troubled with diarrhea if she stays on a smooth diet. The last case has been out of the hospital two weeks and is on a smooth diet, symptom-free.

COMBINED ACTIVE IMMUNIZATION FOR DIPHTHERIA AND TETANUS*

A PLEA FOR ITS ROUTINE USE

By JEAN V. COOKE, M.D.
St. Louis, Missouri

The value and desirability of routine active immunization of children against diphtheria has come to be generally accepted. In the past twenty years there has been an increasing wave of active diphtheria prophylaxis throughout the United States in which both urban and rural communities have participated. The practical results of this are evident in many places by the considerable decrease in the number of cases of clinical diphtheria observed. One of the most significant statistical observations of the effect of diphtheria vaccination is found in a recent summary of diphtheria mortality in the United States.[1] In 88 cities with a total population of 37,575,105, there were, in 1936, only 568 deaths, or a mortality of 1.51 per 100,000. These same cities in 1923, with a population of 31,060,848, had 4,078 diphtheria deaths, or a mortality of 13.13 per 100,000. In general it would seem that the evidence is sufficiently convincing to establish the dictum that every child should be vaccinated against diphtheria toward the end of the first year of life or as soon thereafter as possible. The acceptance of this dictum and the continued active cooperation of individual physicians in carrying out diphtheria immunization on all children is the goal to be reached in eradicating the disease.

In recent years, the method of vaccinating against diphtheria has been much improved by

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*From the Department of Pediatrics, Washington University School of Medicine, and the St. Louis Children's Hospital.

the introduction of alum precipitated toxoid. The superiority of this antigen over toxin-antitoxin and plain toxoid is unquestioned. However, the method for its use is not yet entirely settled. The general practice has been to regard a single injection as sufficient for immunization and many reports indicate that a high proportion of subjects receiving one vaccination with alum toxoid develop negative Schick tests. On the other hand, several observers (Frazer and Halpern,[2] Fitzgerald,[3] Park[4]) have pointed out that the antitoxin titer of subjects given the single dose immunization is not always maintained and varying percentages of such apparent immunes have again become susceptible when tested a year or more later. Several cases have come to my knowledge in which children given a single dose of alum toxoid have later developed clinical diphtheria. Experimental evidence indicates that in such immunizations two separate successive antigenic stimulations with a definite interval are necessary to produce regularly a lasting immunity. The antitoxin resulting from the "primary" stimulus may fall to a low level after a few months, but when a second antigenic injection is given, the "secondary" response of antibody production is rapid and the antitoxin persists at an adequate protective level. My own observations[5] in comparing single dose alum toxoid immunization with two doses given with an appreciable interval between them, have shown that the two-dose method, as would be expected from the experimental studies, gives a higher percentage of permanent immunity. It would appear that the ideal method of diphtheria vaccination is two doses of alum toxoid given with an interval of two months, and that a single dose, while producing a permanent immunity in a certain fairly high proportion of those injected, is definitely less reliable than two doses.

Although the effectiveness and value of active diphtheria immunization are in general well appreciated, it is only in the past few years that various experimental observations have shown that, in similar fashion, active immunization can also be produced against the toxin of tetanus. This development came more rapidly because of the known antigenic similarity between the toxins of diphtheria and tetanus and because advantage could be taken of the experience gained in immunization with alum precipitated diphtheria toxoids. The earlier observations of Ramon showing that toxoid-injected animals were effectively protected against many times the lethal dose of tetanus toxin were quickly and regularly confirmed, and more recently the greater effectiveness of alum tetanus toxoid has been apparent. A number of observations have also been made on the active immunization of human subjects by vaccination both with plain or alum precipitated tetanus toxoid, especially in France and America, and the results have been consistent in showing that the antitoxin immunity which regularly develops appears quite analogous to that which follows diphtheria immunization. Unfortunately, there is no simple test for tetanus immunity comparable to the Schick test in diphtheria, and the development of antitoxin must be studied by the rather laborious method of testing the blood serum by animal inoculations. For this reason, the clinical observations have been made on relatively small groups of persons carefully followed during and after vaccination.

In general, the results of tetanus immunization reported by different observers (Ramon and Zoeller,[6] Lincoln and Greenwald,[7] Sneath and Kerslake,[8 9] Bergey and Etris,[10] Moss and Jones[11]) have been in accord, and I shall summarize briefly from one of the most recent studies as an example. There are apparently no persons naturally immune to tetanus toxin analogous to those who have "natural" diphtheria antitoxic immunity so that tetanus antitoxin is not present in the blood of normal subjects before vaccination. Moss and Jones,[11] after giving two doses of tetanus alum precipitated toxoid to each of 28 adults, found that six weeks after immunization all had from 0.05 to 1.0 unit of antitoxin per c. c. In all this titre fell gradually until at the end of a year the content varied from 0.01 to 0.1 unit per c. c. In this connection, it may be mentioned that the unit of tetanus antitoxin is ten times the relative potency of the unit of diphtheria antitoxin, since the former is standardized to neutralize 1,000 lethal doses of tetanus toxin for a guinea-pig, while the latter unit must neutralize only 100 M.L.D of diphtheria toxin. Also, it is generally accepted that while the presence of 0.03 to 0.01 of a unit of diphtheria antitoxin per c. c. in the blood furnishes adequate protection against clinical diphtheria. In tetanus, on the other hand, there is evidence to indicate that 0.004 unit of antitoxin per c. c. furnishes protection. The fact that in the group of immunized subjects mentioned all had 0.01 unit of antitoxin or more a year after vaccination is excellent evidence of a persistent protection. Most dramatic, however, was the immediate effect of an additional injection of alum toxoid on the antitoxin titre of these persons vaccinated a year earlier. Within

a week it had risen from 6 to 200 times the previous level, so that the majority had at least 1 to 2 units of antitoxin per c. c., while a month after this stimulating dose the average potency of antitoxin per c. c. was 3.3 units. This response is far greater than that produced by the injection of 1,500 units of tetanus antitoxin. Sneath and Kerslake[9] observed that the tetanus antitoxin titre in toxoid immunized persons did not fall appreciably during the second year after vaccination and that a stimulating dose of toxoid then produced a prompt increase of from ten to five hundred times in the antitoxin titre.

The antitoxin immunity after tetanus toxoid vaccination usually requires several months to be established. The titre of the blood, also, is not always maintained at a high level, although such a vaccinated person has the ability to produce an additional quantity of antitoxin with great rapidity. Therefore a vaccinated person later exposed to a tetanus infection may be safely given an additional dose of alum tetanus toxoid instead of tetanus antitoxin. Vaccination has been recommended especially for those who are more or less constantly exposed to wounds with likelihood of contamination with soil. This would include farmers, laborers and gardeners, and, of course, children. With the increase in highway accidents, and the necessity for tetanus prophylaxis for all who suffer wounds in them, it might be suggested that the entire motoring public would profit from active tetanus immunization.

In France, tetanus immunization has been practiced more than elsewhere, and Ramon states that no vaccinated person has developed tetanus. Indeed, vaccination against tetanus is now obligatory in the French army just as is antityphoid vaccination and that against smallpox.

To the pediatrician the question of tetanus prevention is of particular interest, since tetanus is apparently more prevalent in childhood than in adult life. In the mortality statistics for 1930, for example, the death rate from tetanus was 1.1 per 100,000 in the United States. Children under 15 constitute slightly less than 30 per cent of the population, yet half the tetanus deaths were in this age group. In spite of this relative prevalence, the actual morbidity of tetanus in children is small, and even though an effective method of active immunization were available, it might be difficult to justify widespread or universal immunization for a disease of such low incidence. On the other hand, the infection is dreaded by all because of its serious character and the ease with which it may develop from slight wounds. The value of prophylactic tetanus antitoxin in preventing the development of the disease is unquestioned, yet all who treat children are well aware of the difficulties in decision as to whether or not antitoxin should be administered in many instances of trivial traumas. While lacerations from highway accidents, powder burns, punctured wounds, and those obviously contaminated with soil may be given serum routinely, it is well known that many cases of tetanus develop from superficial scratches, or cuts, friction burns, and so on, and yet, it is obviously impossible to advise serum for all such injuries. Not only the expense and pain of the injection, but chiefly the relative frequency of serum sickness with its attendant discomforts combine to limit the routine use of prophylactic antitoxin. For these reasons it is apparent that active immunization of children against tetanus is highly desirable if some simple method of its accomplishment were available which would give reasonable assurance of protection in a high percentage of those vaccinated. Such a method has only recently been devised in the combining of alum precipitated tetanus toxoid with the commonly used alum precipitated diphtheria toxoid.

Combined or mixed vaccination involving the simultaneous injection of two or more vaccines or toxoids for the protection of the individual against more than one disease is a well recognized procedure. Probably the most extensively used has been typhoid-paratyphoid vaccination, but in the last few years Ramon and other French investigators have used various other combinations of two or more antigens and believe that where several are combined a higher immunity is produced than when each is given alone. Ramon and Zoeller[12] found, for example, that after inoculating one set of guinea-pigs with diphtheria toxoid, a second group with tetanus toxoid and a third with a mixture of tetanus and diphtheria toxoids, the third set showed a higher antitoxin titre for both diphtheria and tetanus than either of the other groups inoculated with the single antigen.

A recent study by Jones and Moss,[13] who immunized a group of persons with two doses of diphtheria and tetanus alum precipitated toxoids and studied the production of both antitoxins in the blood for a period of months, demonstrated that such mixed vaccination produces antitoxic immunity in man to both toxins, and in apparently no less degree than is obtained by using the toxoids separately.

The use of diphtheria and tetanus alum tox-

oids combined and given simultaneously is now routine in the St. Louis Children's Hospital and the Washington University Children's Clinic. Local reactions following the injections have been of the same mild character as with diphtheria alum toxoid alone and a general reaction quite unusual in children. Parents, when told of the tetanus combined immunization, have welcomed the added protection enthusiastically. The procedure has been to give two injections of the combined vaccine with an interval of two months between them. We have so far seen only two children so immunized who have later suffered traumatic wounds which ordinarily would have required tetanus antitoxin. Both remained well after a stimulating injection of tetanus toxoid was given instead of serum. The combined diphtheria and tetanus alum precipitated toxoid is available commercially or, if one has only the two antigens separately, a dose of each may be mixed together and given at one injection.

The practice of combining tetanus toxoid with the diphtheria toxoid injection is one which has a particular appeal in preventive pediatrics, because it gives an important added protection without additional effort. Its practical value in preventing tetanus will be apparent only if carried out in the same extensive scale as diphtheria vaccination is now advised. It seems likely that as knowledge of the practicability and ease of tetanus prophylaxis when combined with the diphtheria immunization becomes more widely known, physicians and parents will both demand that tetanus toxoid be included in all diphtheria toxoid prophylactic antigens.

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AN EPIDEMIOLOGICAL STUDY OF APPROXIMATELY 400 CASES OF CEREBROSPINAL MENINGITIS IN KENTUCKY WITH OBSERVATIONS ON THE COMPARATIVE VALUE OF MENINGOCOCCIC ANTITOXIN AND ANTIBACTERIAL SERUM*

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and
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In the United States Registration Area, meningococcus meningitis mortality showed a gradual increase from a rate of 0.4 per hundred thousand population in 1910 to a high of 3.9 per hundred thousand in 1917. Beginning with 1918 and continuing through 1922, deaths from this disease steadily declined, reaching a low of 1.0 per hundred thousand population in the latter year. This death rate hovered around 1.0 per hundred thousand from 1922 through 1926, after which another gradual upward swing began.

In Kentucky, the incidence of meningococcus meningitis,§ so far as the records show, followed very closely the trend of the specific death rate in the states in the Registration Area.

This incidence remained fairly high during the three-year period, 1920 through 1922, and then dropped gradually to a low point of one case per hundred thousand in 1925 and in 1926. In 1927, a gradual increase in the incidence of this disease started, reaching the high point of 4.8 cases per hundred thousand population in 1931. This was followed by a gradual decline through 1932 and 1933 to 2.1 cases per hundred thousand in 1934, after which came a sudden rise, beginning

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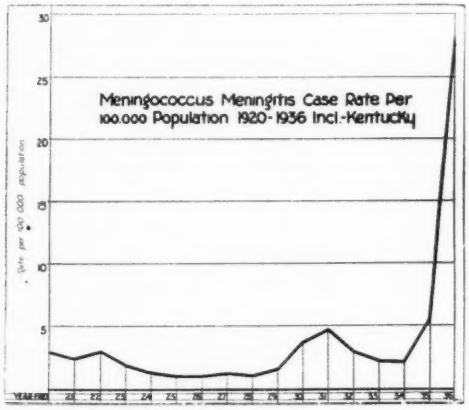
§Meningococcus meningitis was first differentiated from the other meningitides in 1930, and reported and recorded as such.

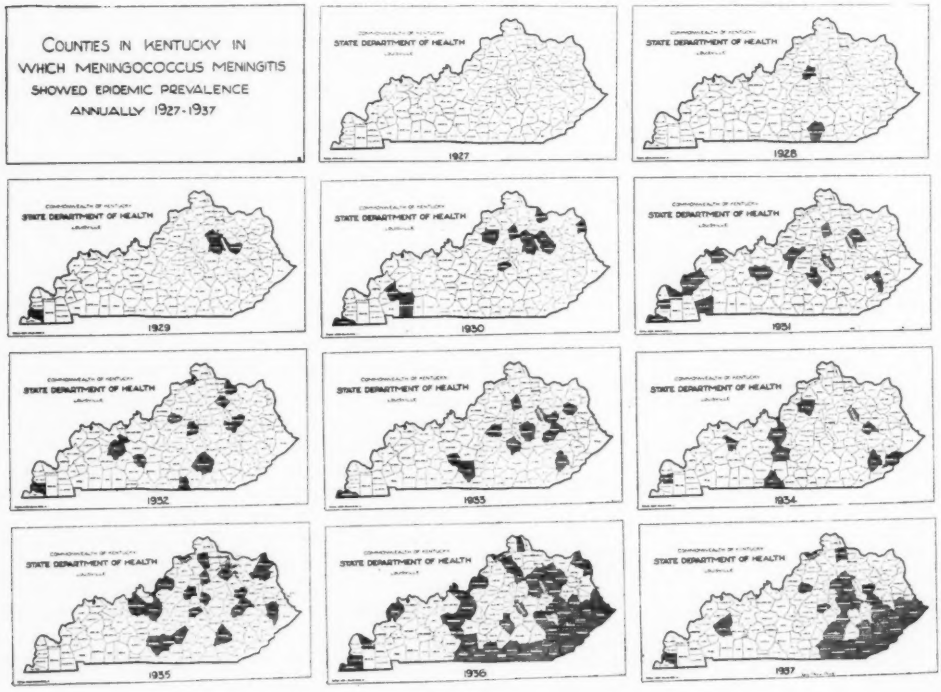
in 1935 and culminating in the widespread epidemic which swept the southeastern section of Kentucky during 1936 and the first several months of 1937. In 1936, incidence of the disease reached an all-time high in the State. From *Graph 1,* the trend of the case rate per hundred thousand population in Kentucky may be seen for the years 1920 to 1936, inclusive.



Graph 1
Annual case rate per hundred thousand population from 1920 to 1936, inclusive.

From 1928 to 1934, one or more outbreaks in which the fatality rate was rather high occurred in various sections of Kentucky. This would indicate that the disease was distinctly different from the ordinary type of endemic meningitis. These outbreaks were usually confined to a single county, although occasionally an outbreak involved one or more adjoining counties.

The number of counties in which these sharp outbreaks occurred gradually increased from two in 1928 to the widespread prevalence of the disease in 1936, when 49 counties were involved. *Graph 2* shows by counties the geographical spread of the disease in the State for the years 1927 through 1936 and the first seven months of 1937. In this graph, the shaded counties rep-



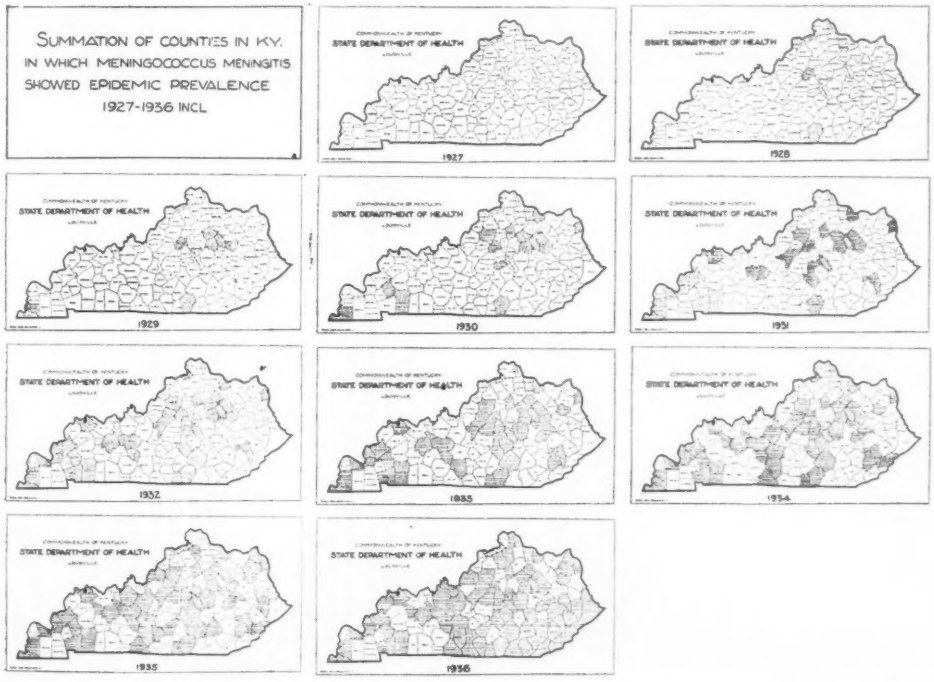
Graph 2
Counties showing an annual case rate of ten or more per hundred thousand population from 1927 through August, 1937.

resent those having a case rate of ten or more* per hundred thousand population.

*With a view to establishing an index of maximum expectancy, above which the disease would be considered prevalent in epidemic proportions in a county, a period covering various degrees of prevalence was selected. The eight-year period from 1927 to 1934, inclusive, was found to constitute such a period. In 1927, 1928 and 1929, the rate of incidence of the disease was fairly low. In 1930, 1931 and 1932, the incidence rate was fairly high; in 1933 and 1934, the rate took an intermediate position between the rates of the two three-year periods. This was thought to represent a fairly good sampling of Kentucky's previous experiences in the prevalence of meningococcus meningitis, as reported and recorded at the State Department of Health. For each of these eight years, a case rate per hundred thousand population was calculated for every county which had experienced any cases of meningococcus meningitis. The median of these rates was then taken for each year, giving eight annual medians. Next, the mean of the eight medians was taken and found to be 7.3 per hundred thousand population. This was felt to be the mean rate of meningitis incidence by county in the State. It was realized, however, that by chance alone the rate in some counties might exceed this mean rate. Hence, in so far as was possible, a rate was established, above which it could be said that the disease definitely prevailed epidemically. Then the standard deviation from this mean rate of the series of eight rates was calculated and the probable error ascertained. The addition of twice this probable error to the mean rate gave what we have chosen to call the maximum expectancy, 9.3 per hundred thousand population. Hence, for the purpose of this paper, any county in which the incidence of meningococcus meningitis reached a rate of 10 or more per hundred thousand population was considered to have the disease in epidemic proportions and was justified in directing more than ordinary effort toward its control. This represents very closely the actual experience of the State Department of Health as indicated by calls for assistance from the county health officers.

From this series of maps, it may be seen that in no county in the State in 1927 did the disease prevail to an unusual degree. However, in 1928, two counties had epidemic outbreaks, one in central Kentucky, the other on the southern border of the State. In 1929, five counties showed an incidence greater than maximum expectancy. One of these was on the far western border of the State; the other four formed a group of adjoining counties in the northeastern section of the State. In 1930, thirteen counties showed epidemic prevalence of the disease; while in 1931, fifteen counties were involved. In 1932, a total of twelve counties had cases above maximum expectancy; 1933, there were thirteen such counties, and in 1934 only ten counties.

In 1935, the number of such counties showed a rather sudden rise to twenty; in 1936, which was the peak year, there was still a greater rise to forty-nine counties. In 1937, January through August, only twenty-nine counties in the State had a case rate that reached ten or more cases per hundred thousand population. In studying the year 1936, the peak year, it will be observed

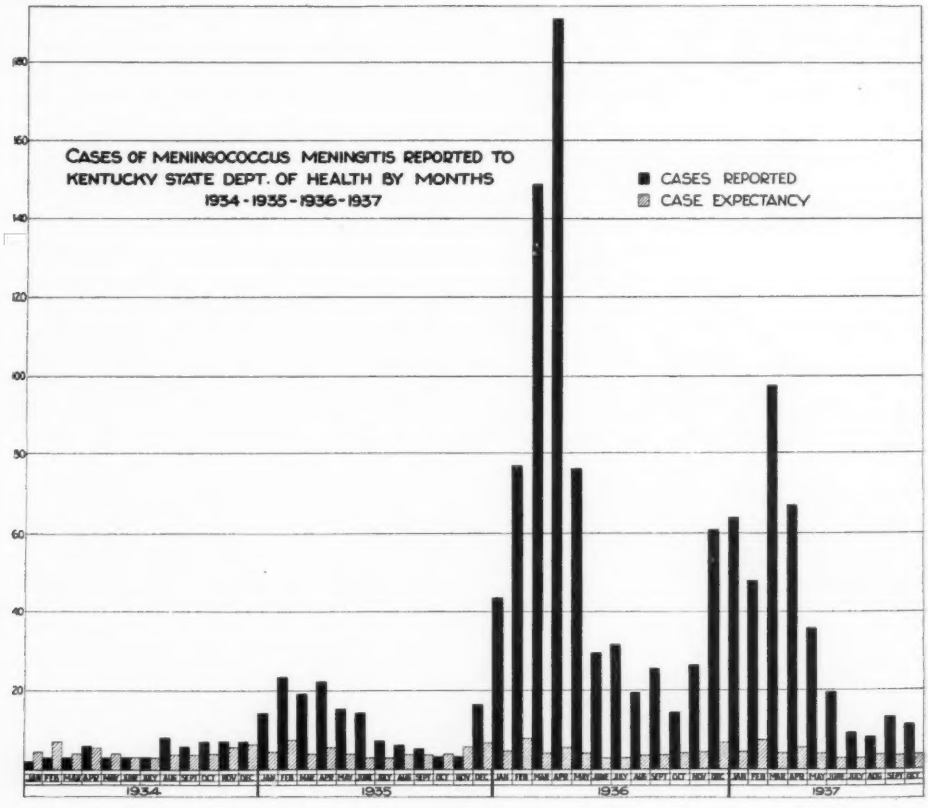


Graph 3

Summation graph, showing the counties having epidemic prevalence of meningococcus meningitis in excess of ten cases per hundred thousand population. These were colored black, year by year, as more counties appeared through the ten-year period from 1927 to 1936, inclusive.

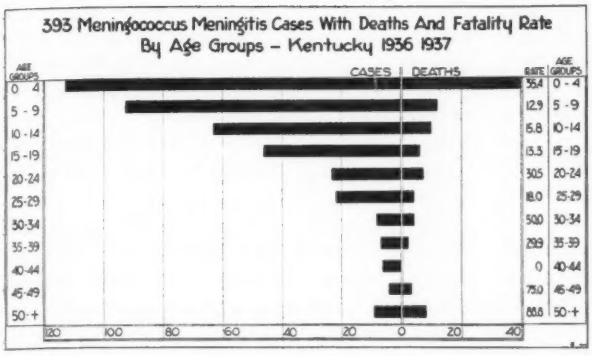
that the area involved embraced a tier of counties extending across the southeastern section of the State to a row of counties extending westward along the southern border to approximately one-half the length of this border. At the western end of this row of counties, a tentacle of the involved counties may be seen to extend northward across the entire State. This tentacle follows a frequently traveled highway. From the eastern end of this band of involved counties, another tentacle may be seen to project in a northwesterly direction across the entire State, likewise following a much traveled route. In 1937, a tendency toward clearing appeared in most of the counties in central Kentucky, where the prevalence of the disease had early manifested itself. However, a marked prevalence of epidemic meningitis still continued along the southeastern and southern borders of the State. This prevalence covered a tier of counties extending to the north section of the State.

It may readily be seen from Graph 3 that during the period 1927 to 1936, inclusive, two-thirds of the counties in the State were "burned over," as it were, by epidemic meningitis, involving approximately three-fourths of the State's population. This graph also shows that the disease formed three early foci, the earliest in a county in central Kentucky, the next in a group of four counties in northeastern Kentucky and the third in one county on the western border of the State. From these three foci, the disease showed a marked tendency to spread from the central and eastern Kentucky foci southward, along the route of frequently traveled highways, and from the far western focus northeastward into counties along another frequently traveled highway.



Graph 4

Cases of meningococcus meningitis reported to the State Department of Health of Kentucky by months from 1934 through August, 1937.



Graph 5
Distribution of 393 cases of meningococcus meningitis, 96 deaths, as to age groups.

From *Graph 4* it may be seen that the months of March and April of the high years of 1935, 1936 and 1937 were the months of highest incidence of meningococcus meningitis in Kentucky.

The incidence of the disease showed a marked decline during the summer months of 1935, 1936 and 1937, but did not return to a point below expectancy.* Among 393 cases in which diagnoses of meningococcus meningitis were made, and case records kept, 96 deaths occurred, a fatality rate of 24.4 per hundred cases. The age distribution of these cases and deaths is shown in *Graph 5*.

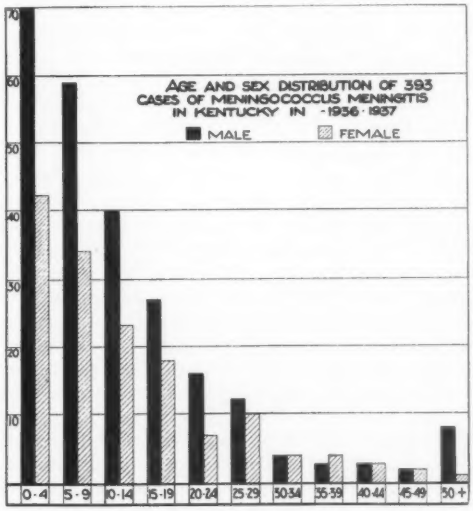
It may be seen from this graph that the greatest number of cases occurred in the age group of 0 to 4, that is, infancy and early childhood, the incidence of the disease gradually growing less as the age of the patients increased, until the upper age brackets were reached, at which period in life the incidence of the disease again takes a marked rise. There was, likewise, a large number of deaths, with a high fatality rate in infancy and early childhood, or 0 to 4 years, the lowest fatality rate obtaining in the age group of 5 to 9 years. Beginning with the 10 to 14 year age group, the trend of the fatality rate is decidedly upward to the age of 50 years and beyond. In the latter group, we find the highest fatality rate.

In the 393 cases on which records were kept, only the American white and Negro races are represented. Cases among whites totaled 351, representing a specific attack rate of 100.3 cases per hundred thousand of the white population of the area involved; 42 cases were Negroes, representing an attack rate of 280 per hundred thousand of the Negro population in the area involved. It is obvious from comparison of these attack rates that that of the Negro race is almost three times that of the white race. It is felt that the poorer hygienic conditions of the homes of the Negro race, rather than a greater susceptibility, is the factor in the higher attack rate.

Among the 351 cases of meningococcus meningitis among the whites, 88 deaths occurred, a fatality rate of 25 per hundred cases, as compared to 8 deaths among the 42 Negro cases with a fatality rate of 19 per hundred cases. Apparently, the fatality rate in the Negro race is lower than in the white race, but not significantly lower.

Distributing the 393 cases into sex and age groups, it may be seen that in the early years of life, from infancy to 24 years, almost twice as many males contract the disease as do females. In the age group of 25 to 49 years, the comparative number of the two sex groups are almost equal, with the males again taking the lead in the group of 50 years or more.

Of the 393 case records, 365 recorded the number of persons in the family group of each case.



Graph 6
Age and sex distribution of the 393 cases of meningococcus meningitis in Kentucky during 1936 and 1937.

*Weekly Public Health Reports, vol. 50, No. 21, p. 702.

This data reveal that 365 cases were members of 295 families, embracing a total of 2,065 persons. This gives a specific attack rate in these families of 17.7 cases per hundred people. Among the 295 families involved, 51, or 17.3 per cent, had multiple cases, 37 of which were families with two cases each, 11 were families with three cases each, one a family with four cases, and two were families with five cases each.

A total of 2,600 postnasal cultures were taken on 2,145 family contacts and convalescing or recovered cases during the months of January through June of 1936. These cultures were taken by nurses and technicians, specially trained in the taking of postnasal cultures. The throats of the cases and contacts were swabbed and plates streaked in the homes of the cases and the inoculated plates transported to near-by emergency laboratories for incubation.

Of the recovering cases and contacts cultured in January, 3.2 per cent were found to be harboring meningococci in the posterior nasopharynx; 2.4 per cent of those cultured in February had positive throats; 6.6 per cent in March; 7.1 per cent in April; 12.5 per cent in May, and 6.3 per cent in June. Thus, it was found that the highest number of carriers was found during the month of May, whereas, the highest number of cases occurred during the months of March and April. However, the carrier rate was high during the months of March and April also. Those whose throats were found to be positive were kept in quarantine until two consecutive postnasal cultures, taken 24 hours apart, were found to be negative. The longest time any throat remained positive was 14 days. It is felt that culturing had very little, if any, influence in lessening the incidence of the disease.

In 1936 and 1937, during which the epidemic of meningococcus meningitis covered a widespread rural area in the mountain section of the State, where laboratory, hospital and other facilities for handling the cases were far from adequate, the physicians and health officers had to rely frequently on diagnoses established by physical and gross spinal fluid manifestations alone. Treatment was frequently administered under most trying circumstances. Case records were often incomplete both from the standpoint of diagnosis and as to the kind, amount and extent of treatment. The 393 cases on which records were fairly complete has been divided into two groups. In the first group, numbering 287, are included cases in which records of treatment administered were complete; the second group, covering 106 cases, comprised those in which the records of treatment were not sufficiently complete, either as to kind or extent of treatment, to permit study.

In the first group of 287, 156 cases were diagnosed on clinical and gross spinal fluid manifestations and the diagnosis confirmed by actually finding the organisms in the spinal fluid by direct smear or by culture of the fluid.

In this group of 156 cases, 33 deaths resulted, giving a fatality rate of 21.1 per cent in the bacteriologically confirmed group of cases. Of these 156 cases, 39 were treated in hospitals with 5 deaths occurring, giving a fatality rate among the hospital treated cases of 12.8 per cent. One hundred seventeen of the 156 cases were treated in farm or mining camp homes with 28 deaths and a consequent fatality rate of 23.8 per cent for the home treated cases.

The remaining 131 cases belonging to the group of 287 cases had adequate clinical and gross spinal fluid findings on which to establish tentative diagnoses, but these diagnoses were not confirmed by bacteriologically demonstrating the organisms in the spinal fluid. For the purpose of the therapy analysis, we will consider only the 156 bacteriologically confirmed cases.

Of the 156 cases, 60 were treated on the first day of illness, with a fatality rate of 11.6 per cent; 40 cases were treated on the second day of illness, with a fatality rate of 20 per cent; 17 were treated on the third day, with an 18.6 per cent fatality rate; 10 were treated on the fourth day with a fatality rate of 60 per cent; 8 were treated on the fifth day with a fatality rate of 50 per cent; 4 were treated on the sixth day with a fatality rate of 25 per cent; and 17 were treated on the seventh day or beyond with a fatality rate of 23.5 per cent. These fatality rates tend to indicate not only that early treatment improves the chances of the patients' recovery but that if patients live beyond the fourth day their chance of recovery also grows better.

The findings on which diagnoses were established in this group of 156 cases were as follows:

SPINAL FLUID

(1) Cloudy spinal fluid	156
(2) Spinal fluid under pressure	149
(3) Meningococcus demonstrated on direct smear	113
(4) Spinal fluid positive for meningococci on culture	72

CLINICAL MANIFESTATIONS

(1) Fever	136
(2) Vomiting	128
(3) Severe headache	134
(4) Stiff neck	113
(5) Retraction of the head	81
(6) Positive Kernig sign	68
(7) Petechial rash	37

Of the group of 156 cases on which diagnoses were established and confirmed, 32 were treated with antibacterial serum with 8 deaths, a fatality rate of 25 per cent. The remaining 124 were treated with antitoxin with 25 deaths and a fatality rate of 20.2 per cent. The difference in the fatality rate in these two groups of cases was not found to be significant. The age distribution of the cases and deaths of both the antibacterial and antitoxin treated groups is given in *Table 1,* together with the fatality rate per hundred cases for each age group.

Table 1

CASES OF MENINGOCOCCUS MENINGITIS TREATED WITH ANTIBACTERIAL SERUM AND ANTITOXIN DISTRIBUTED INTO AGE GROUPS WITH THE NUMBER OF DEATHS AND THE FATALITY RATE FOR EACH GROUP

Age Group	No. Cases Treated, Antibacterial Serum	No. Cases Treated Antitoxin	Antibacterial Deaths	Antitoxin Deaths	Antibacterial Fatality Rate	Antitoxin Fatality Rate
0 to 4	5	40	2	11	40.0	27.5
5 to 9	9	25	1	2	11.1	8.0
10 to 19	7	37	0	4	0	10.8
20 to 29	5	14	0	5	0	35.7
30 plus	6	8	5	3	83.0	35.5
Totals	32	124	8	25	25.0	20.2

When both the antibacterial serum and the antitoxin treated groups were adjusted for age distribution, it was found that there was likewise no significant difference in the fatality rate in the two groups of cases. Each of these two groups of patients were also adjusted for the day of disease on which treatment was started and still no significant difference in the two fatality rates was found.

The 124 antitoxin treated cases received an average of 154.8 c. c. per patient in an average of 4 doses. The minimum amount of antitoxin given to a single patient was 30 c. c.; the maximum amount, 600 c. c. An average of 55 per cent of the total amount of antitoxin given to a patient was given intraspinously; 31.5 per cent intravenously and 13.5 per cent intramuscularly. The average dose of antitoxin given intraspinously was 28.3 c. c., the average dose given intravenously was 34.2 c. c., and the average dose given intramuscularly was 18.5 c. c. The usual frequency of treatment for a patient was every 24 hours.

Of the 32 antibacterial serum treated patients, each received an average of 45 c. c. in an average of 4 doses; 91 per cent of this serum was given intraspinously; 4 per cent intravenously and 5 per cent intramuscularly. The minimum amount given to a single patient was 10 c. c. and the maximum was 205 c. c. The average dose of this serum given intraspinously was 10 c. c., while 15 c. c. was the average amount given intravenously and 15 c. c. was also the average dose given intramuscularly. The frequency of administering this serum was, likewise, every 24 hours.

Of the 124 cases treated with antitoxin, 99 recovered; 37, or 37.3 per cent of these had sequelae. Of the 24 recovered antibacterial serum treated cases, 6, or 25 per cent, had sequelae. Those with sequelae in the two groups manifested the following defects six weeks after recovery:

ANTIBACTERIAL SERUM TREATED CASES	ANTITOXIN TREATED CASES
(1) 50 per cent, defective vision	(1) 27 per cent, defective hearing
(2) 33.3 per cent, defective hearing	(2) 24.3 per cent, severe headache
(3) 16.6 per cent, severe headache	(3) 21.6 per cent, defective vision
(4) 16.6 per cent, relapsed	(4) 16.2 per cent, relapsed
	(5) 10.8 per cent, mentally defective
	(6) 10.8 per cent, very nervous
	(7) 10.8 per cent, paralysis
	(8) 2.7 per cent, defective speech

Forty-two per cent of the antitoxin treated cases gave allergic manifestations, while 18.8 per cent of the antibacterial serum treated cases exhibited similar manifestations.

SUMMARY

Meningococcus meningitis in Kentucky has gradually increased during the last ten years, reaching a peak in a widespread outbreak in industrial southeastern Kentucky in 1936. The season of highest incidence was March and April.

The ages varied from three months to 74 years, as shown by the 393 cases on which case records were kept. The fatality rate was highest in the cases that were over 50 years of age; next highest, in infancy and early childhood, from 0 to 4 years; and lowest in the age group 5 to 9 years. In the first 25 years of life, males were attacked almost twice as frequently as females, the number of cases in the two sexes being almost equal in the second 25 years, while the males again took a marked lead in those over 50 years of age.

Only two races were represented in the cases on which records were kept, the American white and the Negro. The case rate among the Negroes was almost three times that among the whites in the area from which the cases came.

Out of 295 families in which cases occurred, only 51, or 17.3 per cent, had multiple cases.

It was not felt that culturing of throats and isolation of carriers lessened the incidence of the disease in the communities where culturing was done.

In a group of 156 cases in which the diagnoses were confirmed bacteriologically, and accurate treatment records were kept, it was found that the fatality rate was twice as great among those treated in the homes as among those treated in the hospitals. The fatality rate in a group of 124 cases treated with antimeningococcus antitoxin was not significantly lower than the rate that prevailed in a group of 32 cases treated with antibacterial serum. The fatality rate was lowest among those cases which were diagnosed early in the disease and promptly put under treatment.

DISCUSSION (*Abstract*)

Dr. J. C. Knox, Raleigh, N. C.—Those of us who attempt to collect data from the field like those presented by Drs. Blackerby and Caudill can readily appreciate the time and effort necessary for the accumulation of these facts.

In looking through the literature on meningococcic meningitis I have failed to find material with which to compare their findings. The only experience with the disease which gives data on the treatment and some of the epidemiological features of meningitis is reported by Dr. Hoyne (*Journal of the American Medical Association*, volume 104, page 980, issue of March 23, 1937). In his study all cases reported were admitted to the Cook County Hospital, Chicago, and treated in that institution by the method of administering to alternate cases, regardless of color, age, sex, severity of symptoms or length of illness, meningococcic antitoxin and meningococcic bacterial antiserum. The results obtained in this series of cases, the meningococcic meningitis cases admitted since 1934, indicate that the mortality of those treated with meningococcic meningitis antitoxin is only half that of cases receiving antibacterial serum. The factors that ordinarily vary were nearly constant in this study: the same institution, same nursing care, same general type of medical service, same factors of any year that might influence both groups of patients.

From the data presented today certain things are quite apparent: (1) the need for hospitalization of all cases of meningitis. The health officer must make every effort possible to secure adequate hospital care for these cases. (2) Adequate supply of meningococcic antitoxin or antibacterial serum. (3) Close study of existing morbidity statistics to determine an index of prevalence which will indicate the approach of an impending epidemic. If the index as worked out by Drs. Blackerby and Caudill were applied to some of our North Carolina counties we could expect an epidemic in the immediate future.

Dr. Blackerby (closing).—Replying to the question, "Why did we not check the death rate among the meningitis cases not treated at all?" the fact is that fairly complete records were kept on forty-two cases of meningitis which were not treated, but on which the diagnoses were made clinically. In most instances, treatment was not given because the patient refused to be treated. That the diagnoses were not confirmed in these cases is readily admitted, as no spinal punctures were done. All these untreated cases, however, occurred in individuals who were members of families residing in the epidemic area in which proven meningococcus meningitis was occurring. More than that, the large majority of the families in which the untreated cases occurred resided in the immediate neighborhood of other families in which proven cases of meningococcus meningitis were occurring. This being so, it is both logical and reasonable to assume that the chances were that all of these cases were true cases of meningococcus meningitis. Of the forty-two untreated cases, thirty-six resulted in death, giving the tremendously high fatality rate of 85.7 deaths per 100 cases. This fatality rate contrasts rather sharply with the fatality rate of 21.2 deaths per 100 cases that obtained in the 156 serum treated cases discussed in the paper. It is felt that this should serve forcefully to point out to skeptics, and I am sorry to say there are still some in existence, the fact that treatment of meningococcus meningitis with specific sera, whether antibacterial or antitoxic, is highly effective in saving lives. May I further add that, in the area in which this epidemic was occurring, very few cases willing to receive treatment failed to get it, this for the reason that the local county health officer and the practising physicians in each of the counties affected joined hands in seeing to it that adequate treatment was given as promptly as possible to all cases desiring to have it. And all counties in which the disease was epidemic had, with one exception, full-time health departments.

Answering the question, "Was the meningitis death rate among Negroes based upon a limited population or the Negro population of the entire State?" the Negro death rate was based, as stated in the paper, on the aggregate Negro population of the various counties from which the collected case records were drawn and not on that of the entire State.

EVALUATION OF THE SKIN TESTS FOR PREGNANCY*

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The diagnosis of early pregnancy is, of course, the desire of both the patient and the physician, and while we have many signs and symptoms of pregnancy that can be elicited as the pregnancy advances, none until recently has been definite enough in the very early stages of gestation.

The development of the biologic test for pregnancy by Aschheim and Zondek has answered the demands of both physician and patient, for now we can most certainly state in at least 95 per cent of cases whether pregnancy does or does not exist, in the first three weeks.

HISTORY OF THE DEVELOPMENT OF THE BIOLOGIC PREGNANCY TESTS

Stockard and Papanicolaou[1] (September, 1917) found in the vaginae of guinea pigs successive changes of cell types during the sexual cycle, and this is the foundation on which Allen and Doisy[2] (September, 1923) built the test to determine quantitatively the activity of ovarian and placental hormones. Loewe[3] (July, 1925), and Frank[4] (August, 1925) were able to demonstrate the presence of at least one mouse unit of the female sex hormone in 40 c. c. of human blood during the premenstruum and a steady increase of this hormone during pregnancy. Dohrn and Faure[5] (May, 1928) demonstrated large quantities of this hormone in the urine and feces of pregnant women. Papanicolaou[6] (May, 1926) and Corner and Allen[7] (March, 1929) produced experimental proof that the corpus luteum, besides producing the female sex hormone, also produces an inhibitory hormone (progestin), which prepares the endometrium for nidation and gestation. Independently, and almost simultaneously, Zondek and Aschheim[8] (February, 1927) and Smith and Engle[9] (November, 1927) showed that transplants of the anterior lobe of the pituitary into immature mice and rats produces remarkable changes in the ovaries, within three days showing maturation and rupture of graffian follicles (pituitary-A) and leuteinization (pituitary-B); Jacob Hoffman[10] (1927) and later Steinach and Kun[11] (1928) demonstrated that if anterior lobe pituitary transplants were made into old and sexually stagnant mice the sexual apparatus of these animals was reactivated.

Fluhmann[12] (August, 1929) demonstrated anterior pituitary hormone in the blood of patients castrated by operation or irradiation and in women suffering from amenorrhea and other irregularities of menstruation due to ovarian insufficiency. This pituitary hormone is also demonstrated in the urine, and not infrequently renders the Aschheim-Zondek test inaccurate.

In human pregnancy, there occurs so great an increase of ovarian and placental hormones or pituitary-like prolans in the blood and so large an excretion of these hormones in the urine that, on the basis of this increased production and excretion, it is possible to diagnose pregnancy with the aid of animal experiments using mice (Aschheim and Zondek,[13] July, 1928) and rabbits (Freidman,[14] November, 1929).

The basis of the biologic pregnancy tests, therefore, lies in the quantitative and not in qualitative hormonic differentiation of the blood or urine of the pregnant woman as contrasted with the blood or urine of the non-pregnant. This difference is so exceptionally great that it may be considered the outstanding characteristic of the blood and urine in pregnancy. There is no hormone known that appears solely and constantly during pregnancy; therefore, there are no specific hormones of pregnancy.

The department of gynecology at Louisiana State University has conducted the performance of the Aschheim-Zondek test for the departments of gynecology and obstetrics at Charity Hospital for the past five years, and we can heartily second the opinion of all other co-workers in saying that this is the only dependable test for pregnancy so far devised. The cost of the test, the upkeep of the animals, and the time required have made us often wish that some other simpler and less expensive method might be devised. For this reason, we have given all new and simpler methods that seemed plausible a fair clinical trial.

BIOLOGIC SKIN TESTS FOR PREGNANCY

The skin tests for the diagnosis of pregnancy have occasioned some widespread attention in

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the literature and gave promise of success as far as simplicity and speed were concerned.

For more than eighteen months we have made attempts by clinical application to evaluate the various tests as published. This report is a study of the results of the biologic skin tests only. We have also tried out the various other pregnancy tests described in the literature, and we expect to report on them in the near future.

The recent report (September, 1936) on the use of the antuitrin-s intradermal skin test by Gilfillen and Gregg[16] stimulated us to give this method a thorough and complete clinical trial. The theory underlying this test is that the pregnant woman, having an abundant supply of prolan in the blood, should be immune to further injections of urinary prolan, whereas the non-pregnant woman should be prolan-sensitive. It is claimed by the authors that the test is as reliable as that of Aschheim-Zondek, with the obvious advantages of simplicity and economy of time and money; in fact, an office procedure.

Dowell[21] (July, 1933), using antuitrin extract, not antuitrin-s, employed the same technic later described by Gilfillen and Gregg, and speaks of the test as a simple, safe, inexpensive, and accurate test for the diagnosis of pregnancy. He gives no experimental data. Green (July, 1937) also reported favorably on the basis of 59 cases, noting no failures in this group.

That the test is neither new, original, nor reliable can be attested by the following facts:

Porges and Pollaczek[17] first suggested the idea to the Vienna Medical Society in March, 1929, and claimed for the method accuracy and dependability. However, a few months later, after further trials, they reported 18 per cent failures.

In 1929, Albert Mathieu[15] spoke of the intradermal test for pregnancy:

> "This test is quite new; the method consists in injecting the hormone of the anterior pituitary lobe intracutaneously. Pregnant women give no reaction and non-pregnant give a marked skin reaction in from 24 to 48 hours. Prolan is the substance used, and 0.1 c. c. is the amount."

Although Mathieu describes the method, apparently he had had no experience with it at this particular time, as he states that he was not able to obtain prolan.

Deutsch,[18] in November, 1929, described the method as absolutely unreliable on the basis of 45 pregnant and 65 non-pregnant women. Strauss[19] (June, 1930), using the test in 184 cases, pronounced it too unreliable for use in general practice. Schneider and Cohen[20] also report on the basis of 118 tests on 95 females and 23 males. Seventeen of the females were definitely known to be pregnant. They report that the results obtained with antuitrin-s injected intradermally in no way exhibit the reliability of this test as a means of diagnosing pregnancy or gynecologic disorders.

Saglik and Scipiades[23] used the intradermal skin test of Gilfillen and Gregg and proved it 100 per cent negative in pregnant and non-pregnant monkeys as well as in laboratory rodents and in a small control series of 10 non-pregnant and 25 pregnant women, and demonstrated the inferior reliability of the test as compared with the Aschheim-Zondek and Friedman tests.

The Technic.—Two minims of fresh antuitrin-s were injected intradermally in the volar surface of the forearm, using a 26-gauge needle, in all of these tests. An important detail of the test is that no alcohol may be used in the preparation of the syringe, needle, or arm; it is also important that the solution be placed intradermally. The tests were read at intervals of 1/2, 5, and 10 hours. These tests were made only on known non-pregnant women in the medical and gynecological wards and on known pregnant women from the obstetrical wards and clinics. An area of erythema, 25 to 30 mm. in diameter about the site of injection is considered negative for pregnancy and the absence of the reaction within 1/2 hour is considered a positive test for pregnancy.

The results of our tests are as follows:

The control cases gave better results than the pregnant cases, since we could perhaps consider the delayed reaction a delayed negative and add them to our negative series. In the pregnant series, however, the delayed reaction would definitely mean a delayed faulty reaction (because it would be delayed negative), and this brings the percentage far below the acceptable figure.

Analysis of the faulty reactions has given no clue to the reason for it. Nine cases from 15-60 years of age, afflicted with all types of diseases, have given a faulty positive reaction. Twenty-four women pregnant from two to seven months, normal pregnancy or with signs of toxemia or infection, have given faulty negative reactions.

In a total summary, 59.3 per cent of definitely correct results have been obtained, while 9.2 per cent are definitely wrong. The remaining 31.5 per cent gave delayed or doubtful reactions.

From the above figures, it is apparent that the

Table 1

SKIN TESTS IN VARIOUS DISEASES

Diagnosis	Number	Pregnancy	Positives (½ hour)	Delayed Negatives 2 hours	5 hours	10 hours	Negatives
Tuberculosis	93	3	44	30	7	4	49
Menopause	66		23	15	5	0	43
Pelvic inflam. dis.	8		2	1			6
Abortion	5		4	2			1
Cervicitis	3		1				2
Carcinoma	9		1		1		8
Postpartal sepsis	2		1				1
Neuropathies	8		3	1		2	5
Cardiovascular disturbance	20		6	1	3		14
Pregnancy	110	110	85	9	16	1	23
Pelvic trs. and inf.	6		3	2			3
Appendicitis	9		7	4	3		2
Endocrinopathies	10		4	4			6
Upper abdominal lesions	9		2	2			7
Genito-urinary inf.	16		8	2	2		8
Arthropathies	9		1		1		8
Respiratory inf.	6		0	0	0	0	6
Skin diseases	8		3	2	1		5
Postoperatives	4		1	1			3
Systemic infection	12	1	8	6	2		4
Others (cystocele, prolapse, rectocele, etc.)	12		4	3			8

Table 2

AGE GROUPS

Total number of cases	359
15 to 25	120
26 to 35	102
36 to 45	67
46 to 60	52
61 to 75	18

Table 3

PARITY

0	127
1	73
2	47
3	29
4	24
5	14
Above 5	45

Table 4

CONTROL CASES

	Total No.	Percentage
(1) Cases in which reaction appeared 10 minutes to ½ hour after injection Negative for pregnancy	149	60.9
(2) Cases in which the reaction appeared from ½ to 10 hours after injection Delayed negative for pregnancy	87	35.5
(3) Cases in which no reaction appeared Faulty positive reaction	9	3.6

Table 5

	Total No.	Percentage
(1) Positive reaction for pregnancy	64	56.1
(2) Cases in which a reaction appeared from ½ to 10 hours after injection Delayed faulty negative	26	22.8
(3) Cases in which a distinct reaction appeared 10 minutes to ½ hour after injection Faulty negative for pregnancy	24	21.1

Table 6

SUMMARY OF SKIN PREGNANCY TESTS

	Total No.	Per-centage
(1) Total number of cases examined	359	
(2) Correct results obtained	213	59.3
(3) Doubtful results obtained Delayed reactions	113	31.5
(4) Faulty results obtained	33	9.2

antuitrin-s test for the diagnosis of pregnancy and other gynecological conditions cannot be accepted as a very definite factor in these cases. The number of false negatives and false positives together with the number of delayed reactions, negative and positive, make the test highly unsatisfactory.

GRUSKIN'S ALLERGIC PROTEIN SKIN REACTION TEST FOR PREGNANCY

Gruskin[22] reported on a new test for the determination of pregnancy which is based upon a new principle and has the advantage of simplicity of performance plus quick results obtained by its interpretation. The test is based on the homologous proteins' producing an allergic reaction by the formation of pseudopodia when injected intradermally in positive cases. According to the author, the use of placental tissue as an antigen when introduced intradermally, causes pseudopod formation at the site of injection in pregnant females, but none when pregnancy is absent.

The reaction is purely the result of the homologous nature of the protein, because the hormones carried by the placenta are destroyed by heating and play no part in this reaction. As far as we were able to determine, this was an original idea, and we considered it worth trying.

The method used by us was as described by Gruskin in his paper. The antigen was prepared by two different departments, Pharmacology and Biochemistry, and used on separate cases and by different technicians. Because our first results were at variance with the author, we immediately wired Gruskin for additional information, which he gladly volunteered, as well as methods for modification of the antigen. He also sent antigen of his own for use in our experiments. This antigen was used, as well as that prepared by us according to his instructions.

The Test.—The contraindication as pointed by Gruskin was observed, namely: the test was not done during menstruation because the decidual involvement would respond to the homologous protein of the placental extract, giving positive reactions. Also, in order to avoid the possibility that endocrine disturbances or hypersensitive skins might respond to intradermal injections even of a saline, a saline-control injection was made first, and if pseudopods formed, this patient was declared unsuitable for the test.

One-tenth c. c. of the antigen was injected intradermally with a 27-gauge needle with a one c. c. tuberculin syringe, slowly, so that no false pseudopods would form. In positive cases, a slight area of inflammation with pseudopod-formation appears in 10 minutes. In negative cases, no such reaction takes place. The control-saline must always be negative, showing no inflammation and no pseudopods. The bleb after the injection must be perfectly round and give the appearance of "orange peel."

Schwartz,[24] in reviewing the test in 252 cases, states that skin testing with the ordinary technic is, at best, only a relatively crude detector of hypersensitiveness. Many normal skins will exhibit erythema with almost any antigen in any type of intradermal testing and false reactions can be avoided only by paying strict attention to controls. He found the nitrogen content of the Gruskin placental extract to be 0.35 mg. per c. c., with a protein content of 0.221 mg. per cent. Every patient tested with the placental extract was also tested with a control solution of amnion prepared to contain a like protein and nitrogen content as the placental extract. They claim that this solution is superior to normal saline in that it not only determines those skins which show dermographia, but also those which show a non-specific protein sensitivity.

In our work we used only the normal saline control and wonder how much, if any, the use of the saline or the non-use of the amnion solution had to do with our results.

Table 7

Total number of cases 198

	No. Cases	No Reaction	Per Cent of Failures
Known pregnant, white	26	12	32.4
Known pregnant, colored	125	37	
		False	
Known non-pregnant	47	15	31.9
Total per cent of failures			32.3

In the white obstetrical ward, 26 cases of advanced pregnancy were given the test, 12 showing no reaction to the injected antigen.

In the medical wards, 47 known non-pregnant women were given the test, 32 showing a negative and 15 a positive reaction.

In the colored obstetrical ward and clinic, this test was used on 125 patients, 88 giving positive reactions, 37 negative reactions.

After considering the above facts, it is our opinion that the Gruskin skin test for pregnancy is not a reliable routine test for the determination of early pregnancy. It is possible that with better control tests, results more in keeping with Gruskin and Schwartz may be obtained.

This report was made possible by the cooperation of the Departments of Biochemisty and Pharmacology and the untiring efforts of Drs. M. L. Stadiem and L. Seyler, of the Department of Gynecology, and Dr. C. Reynolds, of the Department of Pharmacology. To them we wish to express our sincere appreciation.

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BREECH PRESENTATION*

A REVIEW OF 133 CONSECUTIVE CASES FROM TOURO INFIRMARY

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Breech presentation occurs in about 3 per cent of all deliveries and is characterized generally by a high fetal mortality. It is my purpose in this paper, besides presenting a report of a series of cases from Touro Infirmary, to list a few principles that should be kept in mind in handling this type of case.

This study consists of 133 consecutive cases of breech presentation delivered during the period from July 1, 1933, to January 1, 1937. Both private and public ward cases are included, but only cases delivered in the hospital have been taken because of more accurately kept records. This is a comprehensive study, since these cases are classed not only as "booked," but as "emergencies" as well, inasmuch as our public ward takes care of abnormal cases for two outside agencies. It must be stated here that naturally the operative or active treatment is more prevalent on the public service because of this latter fact, and also because it is a teaching service. No attempt, however, is made to compare this group with the private cases where the more conservative attitude is prevalent.

Number and Type of Cases.—There were 94 primaparas and 39 multiparas. There were 9 sets of twins in the former group and 3 in the latter. Very few multiparas were delivered among the public ward cases, since our resident staff is prepared to take care of these in the home, provided no abnormality exists.

Duration of Labor.—Naturally the duration of labor is somewhat prolonged due to the fact that the soft breech is not so good a dilating wedge as the head. The early rupture of the mem-

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branes which often occurs because of the imperfect filling of the inlet, and which frequently is a source of concern because of the possibility of prolapse of the cord, actually shortened labor. The results are shown in *Table 1.*

Table 1

	Primipara	Multipara
Duration of labor, average	17.5 hrs.	12.3 hrs.
Membrane intact through first stage	20.7 hrs.	14 hrs.
Membrane ruptured at onset or early in labor; spontaneous or artificial	14.1 hrs.	9.2 hrs.

Type of Delivery.—This is a mighty factor as concerns fetal mortality and maternal morbidity. It is the opinion of the author that if breech presentation under close observation were more often treated as a normal left occipito-anterior and the "hands off policy" adopted, the outcome would be far better. As it is, "fear" and "interfere" seem to follow one another and tend to increase complications. In analyzing records, one finds the term "breech extraction" rather loosely used. It should be clearly distinguished from "breech assistance," where the breech is delivered spontaneously and aid is given in delivering the upper extremities and head (*Table 2*).

Table 2

Spontaneous delivery	11	15
Epis. and spon. delivery	23—34	7—22
Epis. and forceps (to breech)	1	0
Breech extraction	14	14
Epis. and breech extraction	51—66	3—17
Cesarean section	3	3

Thus we see that 56, or 38.6 per cent of the cases, were delivered without operative interference (except for episiotomy); while 83, or 57.2 per cent, were breech extractions. This latter figure is high, but due allowance must be made for the misuse of the term "breech extraction." Again, and I quote from Piper,

"It is the consensus of opinion that during labor inaction should be the physician's policy until the fetal body is born to the umbilicus, unless an indication for rapid delivery arises."

There were 6 cesarean sections. The indications follow:

Suspected pulmonary tuberculosis, pleurisy with effusion, contracted pelvis	1 case
Breech with contracted pelvis	2 cases
Prolapse of the cord	1 case
Marginal placenta previa	1 case
Previous section for generally contracted pelvis	1 case

Puerperal Morbidity and Mortality. — The term "puerperal morbidity" here implies a temperature of 100.4° or over for any two days postpartum, exclusive of the first 24 hours. Temperature readings are done every 4 hours. A total of 25 cases, or 18.7 per cent, came under this heading. Seventy-two per cent of these cases followed operative treatment, while 18 per cent followed spontaneous delivery with or without episiotomy. Watson[2] says that in Sloane Hospital for Women the morbidity rate was 18 per cent for 3,456 cases, using the same standard as used here.

There were two maternal deaths (1.5 per cent) in this series. One patient was admitted with suspected pulmonary tuberculosis and died on the fifth postpartum day following a cesarean section done under spinal anesthesia. The other death was a case of hypertensive heart disease that developed acute pyelonephritis and pneumonia and died on the second postpartum day following a bag induction and breech extraction.

Fetal Mortality and Non-Fatal Accidents.— There were 145 babies born to 133 mothers. Eighteen babies were lost, representing a gross fetal mortality of 12.4 per cent. The corrected mortality, which excludes babies weighing less than 2,500 grams, macerated stillbirths, antepartum deaths, and monsters, was 5.2 per cent, there being 7 in this group. The cause of death was:

Tentorial tear, intracranial hemorrhage	2 cases
Prolapsed cord	1 case
Cause undetermined, no autopsy	4 cases

Of these 7 deaths, 6 were listed as breech extractions; and only one as a spontaneous delivery. Various authors[3] [4] [5] [6] place the gross mortality figure at 10 to 25 per cent and the corrected 5.2 to 7.4 per cent.

There were 3 non-fatal accidents, including 2 cases of fracture of the femur, and one case of intracranial injury that was discharged improved at three weeks.

Rules for breech presentation:

(1) When a breech presentation is found in the last 4 weeks of pregnancy, suspect and attempt to rule out an abnormality such as contracted inlet, placenta previa, multiple pregnancy, or fetal monstrosity, the x-ray should be used when in doubt. The pelvic measurements should be carefully checked.

(2) Williamson,[7] Moir,[8] Kitchen,[9] and others

recommend external version prior to the onset of labor. At Touro Infirmary this procedure is not advocated.

(3) Due to prolonged labor and greater likelihood of maternal exhaustion, analgesics should be given judiciously during the first stage. Carbohydrates and fluids, given together as fruit juices, will limit the tendency to acidosis.

(5) Watchful waiting is necessary. Check the fetal heart tones often.

(5) The mother should be carefully coached after full dilatation of the cervix so that the expulsive pains may be used to advantage. Gas analgesia should be begun.

(6) Be prepared to resuscitate the baby should it be necessary.

(7) Iron out the perineum well and make a liberal episiotomy in primiparas when the breech is on the perineum.

(8) Allow the patient to push the breech out.

(9) Should one or both arms become extended, use Potter's technic of rotating and re-rotating the body.

(10) In bringing the head into the pelvis, keep the sagittal suture in the oblique or transverse diameter of the inlet, as here the diameters are larger and extension of the head is less likely to occur.

(11) Use Piper's forceps if the head does not come easily.

(12) If labor has been long and tedious, the uterine musculature may be exhausted. Therefore, give posterior pituitary extract immediately after the birth of the child to prevent atony and undue bleeding.

The following precautions should be observed:

(1) Do not give posterior pituitary extract at any time during labor until delivery occurs.

(2) Do not hurry the operation at any time. Remember, fetal death from asphyxia occurs infrequently as compared to that due to intracranial injury and hemorrhage as a result of haste.

(3) Do not make pressure over the shaft of a fetal long bone if possible. Select a joint where flexion normally occurs. On the other hand, it is better to have a live baby with a fractured humerus or femur, than a dead baby with all bones intact.

(4) Do not make undue pressure over a viscus. Rupture may result.

(5) Do not allow the baby's head to be born too rapidly. Severe perineal laceration and intracranial injury may be the price.

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SOME PRACTICAL CONSIDERATIONS RELATIVE TO COMPLICATIONS OF MASTOIDITIS*

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In this paper we are considering those complications which the average otologist encounters in practice in the city with a population between fifty and one hundred thousand. These problems have been very real to us. They have probably occurred to you, and we feel that an exposition of our methods of dealing with them and the resulting outcome is timely.

By far the simplest and most common associated condition of both an acute purulent otitis media; and, hence, an early mastoiditis, and one which appears for the most part to be conscientiously neglected by many otolaryngologists, is a simple sinusitis. In our experience over 90 per cent of our otitis medias are suffering from either an infection of one or more of the accessory nasal sinuses. Most commonly the antra are the offending factors, but, not infrequently, a pan-sinusitis is found. Hence, in all early cases of mastoiditis this complication should be searched for and cleared up by treatment. This is preferably done by irrigation via the natural orifice. In several instances with such therapy the signs of early mastoid involvement have subsided as the sinus or sinuses have returned to their normal status. Subsequent follow-ups and audiograms have revealed that such ears have had no residual changes and that the hearing was practically normal.

The simplest mastoid complication *per se* is a

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cortical perforation, which is easily confused with either skin, or scalp infections with a secondary lymphadenitis, or external otitis which may present several of the cardinal signs of mastoiditis. This constitutes one of the most baffling diagnoses that the otologist is called upon to make; and not a few normal mastoids are explored, needlessly, when a simple study of the case would have prevented the same. Let us look into these cases more closely.

First in etiological importance of these pseudo-complications are inflammation or infections of the external auditory canal wall. These may consist of either excoriations self-induced by the patient with a blunt object such as a bobby-pin, or excoriations instigated by the discharge from an acute purulent otitis media, or by an actual furunculosis.

Second in importance are either scalp infections or skin infections of the pinna, such as eczema or impetigo. These are usually accompanied by a secondary posterio auricular lymphadenitis which may break down rendering the picture of a true cortical perforation.

Third in this group is a relatively new complex which is becoming more and more a potential factor in diagnosis of a cortical perforation. This is the reaction which invariably follows the improper use of x-ray therapy of an acute mastoid. Overdosage results in many or all of the features exhibited by an early cortical perforation.

The pathology and symptomology of this group of cases is that of a cortical perforation and the chief difficulty lies in making the differential diagnosis. They consist of a posterior auricular edema which may be similar to cortical perforation, as even fluctuation may be present if a secondary posterior auricular lymphadenitis has broken down. The fundus or tympanic membrane may be impossible to visualize in the case of furunculosis, and this may be misconstrued as a sag of the posterior superior segment of the canal wall. The soft tissue tenderness in the case of cellulitis may extend over the entire bony portion of the mastoid, and if the examiner is not careful, interpreted as bony tenderness. The edema may simulate the picture with which most textbooks of otology are wrongly decorated as that of an acute mastoiditis; namely, that in which the pinna is pushed far forward.

In diagnosing a true cortical perforation from the above mentioned pseudo conditions, the following facts are well borne in mind. First, even in a true cortical perforation externally, surgery is not imperative immediately and a day or two lost in making an accurate diagnosis is merely prolonging your patient's discomfort for a short time; but may save him greater suffering in the long run. Hence, wait until you are reasonably sure of the diagnosis before proceeding with the operation.

Second, the x-ray is of little or no value in these cases, because it will be cloudy from a cellulitis, broken-down secondary lymphadenitis in the pseudo complications as well as in the actual cortical perforation.

Third, the most accurate diagnosis can be made from a careful history and by waiting, and treating the local condition. In the case of a furunculosis, or an external otitis, an alum acetate pack placed in the external canal will either within forty-eight to seventy-two hours reduce the edema or bring the furuncle to fluctuation, when it may be incised. In many instances after such a procedure a sound tympanic membrane may be seen in twenty-four hours which aids greatly in the final reckoning.

In the case of scalp or skin infections, local therapy of the proper type will with the above time period render the diagnosis.

Lastly, in the case of an x-ray therapy reaction, a wait of forty-eight hours will reveal a complete amelioration of the symptoms and usually of the underlying mastoiditis.

However, in this group of cases, too long a wait is not advocated, for in several instances a cortical perforation may be missed even in face of an exploratory incision, and an acute mastoid cavity not evacuated. Hence, after forty-eight to seventy-two hours, if the local condition does not respond to therapy, an exploratory incision should be made. This may be done in two steps. The first going merely through the skin down to the periosteum. If pus is encountered we feel reasonably sure, according to Woodward, that the condition is purely local and the mastoid is not involved. However, should no pus be found in this superficial incision it should be extended through the periosteum where the presence of pus is definite indication of a mastoiditis. If the periosteum is pathological, and in the presence of the above symptoms, even though actual pus is absent we strongly recommend exploration of the mastoid for a microscopic perforation may exist, which if overlooked would result in the lack of drain-

age of a dangerous mastoiditis. In making these incisions the surgeon should be fully prepared with instruments, nurses and assistants to perform a complete mastoidectomy.

The third group of mastoid complications of which the otologist is becoming weary of reading in the literature is the blood stream infection or sinus thrombophlebitis. Nearly all clinics have reviewed and reported cases upon this complication in the last five years, even though there has been little or no change in its conception over that advanced by Braun in his excellent monograph upon the subject (published by Paul Hoeber, Inc., New York, 1928). Our eleven cases, nine of which recovered, follow the general rule and we shall add only several significant facts. A complete ligation consisting of the jugular, and anterior facial vein was performed in all the recovered cases, and free bleeding was secured from the central end of the lateral sinus. The jugular was severed between ligatures as well. In the light of our present knowledge the latter procedure may be dispensed with. Delay in operation is not so serious in this complication as in the other intracranial conditions which result from an acute mastoiditis. We feel that this may occur more frequently as a complication in operations upon an acute otitis media than in those cases where a sufficient time is allowed to elapse for the mastoid to localize and immunity to establish itself in the mastoid cavity before the initial operation. In other words, you will have fewer postoperative complications of sinus thrombosis if you wait two to three weeks before doing the simple operation than if you do the same in two or three days after the initial myringotomy. In one case of our series we found a lateral nystagmus three days postoperatively which was probably due to a toxic irritation of the labyrinth. This cleared up in three days and the labyrinth has since been proven normal by caloric tests as well as the audiogram.

McCarthy, in a paper before the West Virginia State Medical Association (Ear, Nose and Throat Section) in 1934, advocated leaving a long ligature upon the cephalic section of the jugular vein when it was resected, in order to find it more readily for irrigation. We have done this in four of our cases, but have found it to be of more value as a drain for the cervical wound than as a guide to the central jugular segment.

The Tobey-Ayres test is of value only in the normal individual. Too much stress must not be laid upon it as it is normal if the petrosal sinuses are large enough to carry off the blood flow from the lateral sinus, and also in the case of a small mural thrombosis. It may be falsely positive as reported many times in the literature if there is an anomaly of the lateral or sigmoid sinuses. Hence, the test is at best only a physical sign and should be treated as such.

Sulfanilamide offers some aid in a sinus thrombosis, but how much will be determined only by more research.

We are prepared this winter to study the blood sedimentation rate in regard to purulent otitis media, catarrhal otitis media, acute and chronic mastoiditis and sinus thrombosis which we feel will make the diagnosis of these conditions easier, but, to date, so little of our work has been done that any analysis of results would be fallacious.

Next to be considered is the common group of otitic meningitis. From an otological standpoint it consists of a simple extension of the septic process within the middle ear to the meninges. This may be either by a simple erosion of the internal cortex, a rupture of a petrosal cell, through the diploic veins, or via the internal meatus through the labyrinth. In all cases of meningitis in the presence of a purulent otitis media, excepting only those cases in which the micrococcus meningitidis is definitely proven to be present, we urge, as advocated by Eagleton, that an immediate radical mastoidectomy be performed with a complete removal of the cortical plate and such drainage as is possible be established. To support this contention, we cite a case which occurred in 1935.

A boy, aged 4 years, was first seen in the Huntington Baby Clinic, April 20, 1934. At this time he was suffering from a right acute purulent otitis media in which the organism was the Streptococcus hemolyticus. A tuberculin test made at this time was positive. The ear responded readily to local measures and remained dry, the tympanic membrane being completely regenerated. On September 27, 1934, a general tonsillectomy and adenoidectomy was performed, and at this time both ears were normal. The child was not seen again until September 4, 1935, when both ears ruptured spontaneously, while he was suffering from an acute rhinitis. Again the *Streptococcus hemolyticus* was found in the ear culture. Conservative measures were instituted and on October 1, 1935, both ears were found to be dry, with complete regeneration of the left drum head and a partial closure of the right. The temperature was normal throughout this period. Three days later the child was admitted to a local hospital with all the symptoms of a diffuse meningitis. He had marked opisthotonos; a retracted and rigid neck and spine, and practically rested upon his occiput and heels in the dorsal position.

The right auditory canal showed a slight serous discharge in which the short chain streptococcus was found. A spinal tap was performed, revealing a turbid fluid under 260 mm. of water pressure. A cell count revealed 23,750 cells per cu. mm., of which 68 per cent were polymorphonuclear in character. Upon smear, numerous streptococci were easily found in all the microscopic fields. The next morning a thorough radical mastoidectomy was performed with a complete removal of all the dural and sinus plate. Practically no pus was encountered during the procedure. However, on the following morning the rigidity of the neck was gone and the child made an uneventful recovery. This sounds as startling as some of the results we read of after sulfanilamide, but remember it was long before this drug was in common use. Today the child has a dry mastoid cavity and is well except for a tuberculous hip, which is in adequate orthopedic hands.

We have two other cases of similar character but the results were not so outstanding as in the above. However, we feel that even one such recovery is sufficient ground to warrant our assertion that all meningitis with an acute purulent otitis media should be operated upon immediately, and with sulfanilamide, our chances of clearing them up are augmented.

Petrositis next engages our attention. Unfortunately, we have only one fatal case in our records of the Gradenigo's syndrome. This occurred during scarlet fever and even though every effort was made to reach the petrous apex and drain the pus, all attempts were futile. We feel, however, that early operation offers the only chance of recovery in these cases, and that either the burr method, as reported by Kopetsky and Almour, or the old subdural route to the petros apex will suffice, the choice resting upon the operator who must be guided by his experience.

The next complication upon the list is that of brain abscess, either extra or intradural in character. Unfortunately, as otologists, we must admit that by far a too large percentage of these cases are the result of improperly performed mastoidectomies. The most commonly offending organism is usually the type three pneumococcus and in those cases, which have come into our hands, has eroded through the cortical wall from an incompletely cleaned out sino-dural angle cell. In our series a complete removal of the internal table and incision of the dura has resulted in one recovery. Here again early operation is most imperative and one case, apparently, at autopsy might have been saved if an early operation had been instituted. It is distressing that frequently the condition masks its symptoms until the favorable operative period has passed.

Lastly, we arrive at that group of mastoid complications which involve the labyrinth. The diagnosis must be accurately made and either the radical or one of the several labyrinthine operations performed. Personally, we feel much as an early otologist did who stated in his textbook that "the average case of acute purulent labyrinthitis is safer in the hands of an internist than in the hands of the otologist." However, many recoveries are reported in the literature and labyrinthectomy should be instituted in given cases. The accepted teaching is that the radical mastoid operation is indicated early in all of this group.

In closing we wish to summarize several of our suggestions, knowing full well that no conclusions should be drawn from only a few hundred cases. First: in all early acute mastoid patients, the accessory nasal sinuses be thoroughly examined and if infected they should be cleared up by treatment. Second: in all questionable cortical perforations, a diligent search be made for scalp and other external lesions, as these may simulate the above mentioned mastoid complication and lead to needless surgery. Third: in most intracranial complications the prognosis is better in direct proportion to the lack of time allowed to elapse from the onset of the complication and operation. This, we feel, is less true in the case of a sinus thrombosis than in the others.

DISCUSSION (*Abstract*)

Dr. L. Chester McHenry, Oklahoma City, Okla.—Many cases of otitis go on to surgical mastoiditis which would not do so were the accompanying and complicating affections of the sinuses and nasopharynx properly treated at the onset of the otitis.

The differential diagnosis of acute mastoiditis from conditions with which it may be confused is not ordinarily difficult, but may at times be very difficult indeed. A careful history, if one can be obtained, may by simply giving the chronological sequence of events and symptoms, lead one to a correct diagnosis. There is no substitute for a meticulous examination of the patient. At times, as Dr. Moore has brought out, a proper examination cannot be made until an inflammation of the external auditory canal or of the tissues overlying the mastoid has subsided. These conditions must be treated in any event and they ofttimes are causing the patient much more distress than a more serious underlying mastoiditis. Next to the history and physical examination the x-rays are of great value. If soft tissue disease obscures proper visualization of the mastoid in the usual type of film the use of Dr. Granger's antero-posterior position will give better information as to its condition. Serial films are of course of greater value than single films.

We have had no experience with x-ray therapy of acute otitis or mastoiditis. The primary reaction of

tissue to strong irradiation is swelling. This is later followed by breaking down of tissue. In a closed bony cavity such as the mastoid whose contents are already presumably swollen the bringing about of more swelling without first providing mechanical means for the relief of pressure would seem to be extremely dangerous. When mechanical drainage is indicated surgery is necessary, and once surgery is properly performed, there is no need for irradiation.

In considering the formidable quartet of complications of simple mastoiditis: petrositis, sinus thrombophlebitis, brain abscess and meningitis, we feel that an essential therapeutic measure should be at least drainage of the primary focus of infection, the mastoid. If and when the patient's condition permits, this should consist of complete exenteration of cells and the following of infection in the bony tracts to wherever it may lead.

The treatment of petrositis consists of adequate surgery by whatever route of approach is best fitted to the individual case.

In lateral sinus infection with septicemia the sooner the feeding of bacteria into the blood stream is stopped the better will be the patient's chance of recovery. We feel that in cases where the diagnosis has been made it is safer to ligate the jugular vein before opening the sinus. In suspected sinus thrombophlebitis the mastoid should be operated upon promtply. By this means the diagnosis may be made more readily, further treatment may not be necessary, and in the event that it is necessary, the first stage will have been already performed. Of course, we see patients whose condition will not permit operation. The use of general supportive measures plus blood transfusion and sulfanilamide may enable us to bring such patients to a condition in which they may be safely operated upon.

Just a word about sulfanilamide. We have found it of very great assistance in several cases. Dr. Perrin H. Long, of Baltimore, stated yesterday before the Pediatric Section of this Association that he had records of forty-two cases of streptococcic meningitis with thirty-six recoveries under sulfanilamide therapy. No comparable results in this condition have heretofore been reported. Any therapeutic agent which will produce such results in a condition which has been accompanied by at least a 90 per cent mortality demands our attention. The criteria as to dosage and the methods of evaluating signs and symptoms indicating untoward effects are rapidly becoming better defined. In combating the serious conditions which complicate mastoiditis we feel that it is a most valuable weapon.

Dr. M. P. Boebinger, New Orleans, La.—Many complications may accompany mastoiditis. Recently a patient of mine, a little boy 5 years old, with double suppurative otitis and double mastoiditis, whose parents refused operation, developed a retropharyngeal abscess. This was incised and drained. Much to my surprise, he made an uneventful recovery.

Dr. Louis Daily, Houston, Tex.—I fully agree with Dr. Moore that ligation of the internal jugular vein, removing the thrombus, establishing free bleeding in the lateral sinus from below and above, is the operation of choice. If the ligature is attached to the proximal end of the vein outside of the wound for ten days or two weeks, the vein can be picked up and the bulb can be irrigated along the vein in case infection develops in the bulb, thus avoiding the various radical operations recommended for this complication.

Dr. Moore (closing).—I feel that with the advent of sulfanilamide we are upon the threshold of a new era in otitic surgery. As we learn more about this drug, its uses and limitations, we shall be able to modify in a conservative way our operations upon mastoid complications. Probably the next five years will change our viewpoint from one of dread to one in which these complications will be held in less awe than they are today.

HYPOGLYCEMIC THERAPY IN PSYCHOSES OF LONG STANDING*

STUDIES OF BLOOD SUGAR AND BLOOD CHOLESTEROL WITH CASE REPORT

By H. D. Allen, Jr., M.D.
Milledgeville, Georgia

In the eleven months from November, 1936, to October, 1937, I have submitted twenty-nine psychotic patients to treatment by insulin shock. The method followed was that of Sakel as I interpreted it from a translation of the original description published by Sakel and his coworker, Dussik.[1] The psychoses were, in most cases, of long standing.

Twenty-two patients received full courses of treatment, administered with the hope of securing remission of all active psychotic symptoms. The remaining seven patients were treated with the object of testing the effect of the treatment on certain symptoms and on certain elements of the blood chemistry.

The group of twenty-two cases treated for complete remission is made up of twelve cases reported last June at a meeting of the Sixth District, Georgia Medical Society, and to be published in the *Journal* of that Society, and of ten additional cases, treated since that time.

Of these twenty-two cases, sixteen have given favorable responses, showing gratifying amelioration of active psychotic symptoms. In five cases I failed to obtain satisfactory response, and one case relapsed after initial improvement.

Of the five patients set down as failures from the start, two have been transferred to state hospitals and one has been returned to her home with only the slightest possibility that the family will be able to care for her there. A fourth patient has shown some improvement after fourteen weeks of treatment, but this improvement is never sustained for longer than a single day

*Read in Section on Neurology and Psychiatry, Southern Medical Association, Thirty-First Annual Meeting, New Orleans, Louisiana, November 30--December 1-2-3, 1937.

after the treatment is interrupted. The fifth patient has shown an extraordinary degree of resistance to insulin. She was given a course of treatment lasting ten weeks, followed by a full week's rest, then six weeks more of treatment, followed by six weeks' rest, and has now been four weeks longer under treatment. It is only during the current course of treatment that she has had good comatose reactions. The afternoon responses from full coma have, however, been no better than when the reactions were less severe. This patient has responded from an almost vegetative existence to a condition in which she eats voluntarily, dresses herself, goes for walks and shows fondness for her nurse. Previous to the treatment, she had been tube-fed for a period of seventy-two weeks and her only reactions from the vegetative were sullen resistance to necessary attention and occasional outbursts of assaultiveness and destructiveness.

In the seven patients treated to test the effect of the therapy on special responses, the duration of psychotic symptoms had ranged from three to thirty years. In this small group, the following observations have been made: In three patients who have been hospitalized in psychiatric institutions for nine years, sixteen years and more than thirty years, respectively, minimum insulin reactions lasting two to three hours have been found to bring about an amelioration of violent outbursts. In the fourth patient, a case of a most rigid catatonic reaction type of ten years' duration, insulin shocks improve the appetite, allow feeding without a struggle, and lead to the patient's eating voluntarily at other meals, with resultant improvement in nutrition. Two other patients, with psychoses of three and six years' duration, respectively, have shown responses which lend encouragement to the expectation of striking improvement under systematic treatment, and this is being undertaken. In the seventh patient of this group, with a hebephrenic type reaction of nine years' duration, the treatment was abandoned on account of distressing nausea and vomiting following administration of glucose. This patient, however, seemed no worse off for having had the interrupted treatment.

In this group of seven patients special studies were made of the responses of the blood sugar and blood cholesterol in the hope of obtaining light on certain problems which were coming into prominence with accumulating experience. Before starting my first two patients on the insulin shock treatment, I tested them with epinephrine for blood sugar responses. At the same time, I tested similarly several patients with psychoses of very long standing and with extreme deterioration. The three charts in *Fig. 1* show the responses of the blood sugar to epinephrine in these two patients, with psychoses of two and five years, respectively, and in a patient with a psychosis of twenty-two years' duration with much deterioration. In the first two patients the test with epinephrine was followed by administration of a test dose of insulin, with hourly determinations of the blood sugar, which are shown in *Fig. 2*. On subsequently treated patients both blood sugar and blood cholesterol determinations were made concurrently in specimens of oxalated blood at arbitrarily spaced times. The reverse shifting of the sugar and cholesterol was interesting but not proportional (*Figs. 3* and *4*). The colorimetric readings of the cholesterol were done by the Bloor method. All sugar determinations were by the Folin-Wu method. One of my associates (E. W. Allen), who was treating a group of chronic deteriorated patients, began starting off the insulin shock treatment in these cases with a glucose tolerance test with combined sugar and cholesterol determinations from the oxalated blood, and observed this unexpected phenomenon: a direct and parallel shifting of the sugar and cholesterol. *Figs. 5, 6* and *7* show findings in studies made on two typical schizophrenics, two typical recurrent maniacs and two normal controls. I have not had occasion to check the reversal of reactions between the blood sugar and the blood cholesterol in normal persons, and it may be that this response is in no way dependent upon any disturbance in the subject's mentality but is related to a purely biological condition. The suggestion, however, seems warranted that the trend of shifts shown by concurrent cholesterol determinations after administration of epinephrine and glucose promises to be of some value in prognosis or in biological grouping.

A limit is set to the elaboration of biochemic studies in psychotic cases under hypoglycemic therapy by the fact that too frequent venipunctures disturb the patient and unfavorably influence the desired insulin reaction. This, aside from the practical considerations imposed by the limited laboratory force, prevented sufficient checks on the chemical findings in my cases. The whole blood cholesterol determinations offered particular difficulty because of an extra-

neous pigment present at times. Hence, only the very chronic patients, not under systematic treatment, were given repeated tests.

The charts which I have used in illustration were selected as showing most definitely the trends in shifts of the cholesterol and sugar rather than constancy of blood findings, as we recognized the variability of the blood sugar and have assumed the existence of a similar variability of the blood cholesterol.

No attempt will be made at classification of the psychoses treated. To quote from the report of Isabel G. H. Wilson's[2] investigation:

"Schizophrenia is not a clear-cut disease. Around a focus of indisputably recognizable cases there is a sphere in which diagnosis is a matter of opinion."

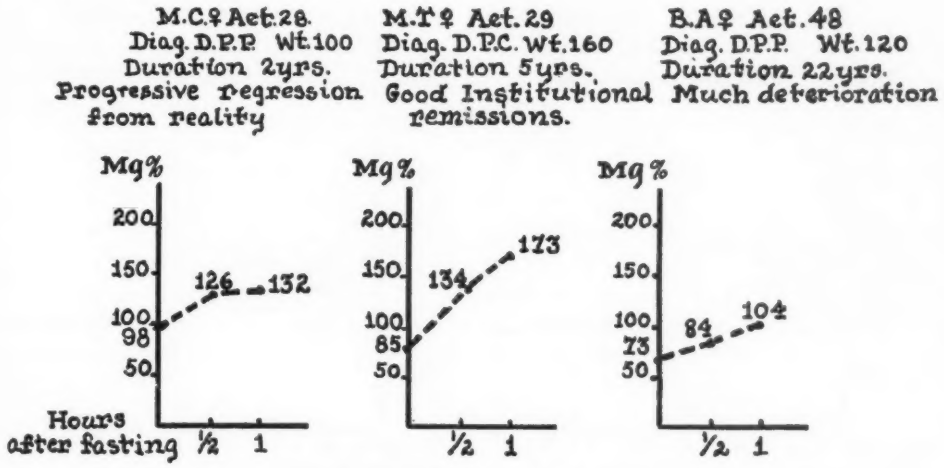

Fig. 1 Responses of blood sugar to epinephrine HCl 1-1000, 1mn. to each 10lbs. body wt.

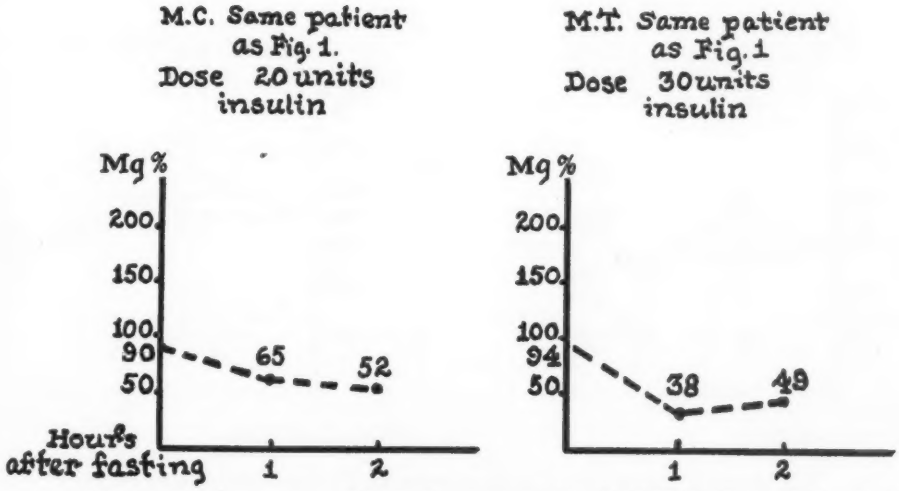

Fig. 2 Responses of blood sugar to initial dose of insulin

In my few recent cases only one was indisputably recognizable as schizophrenia. Treatment was commenced in the fourth month of illness. The patient's reactions were all that could be desired in depth of coma. Yet there was increasing oiliness of the skin, persistent acne and emotional deterioration manifested in indifference to excretions and to arrangement of clothing, in scattering of expressed ideas and in periods of sitting in dream-like attention at the window and mumbling as if in response to auditory hallucinations. This deterioration was accompanied by a decided loss of antagonisms and of assaultiveness and destructiveness, which

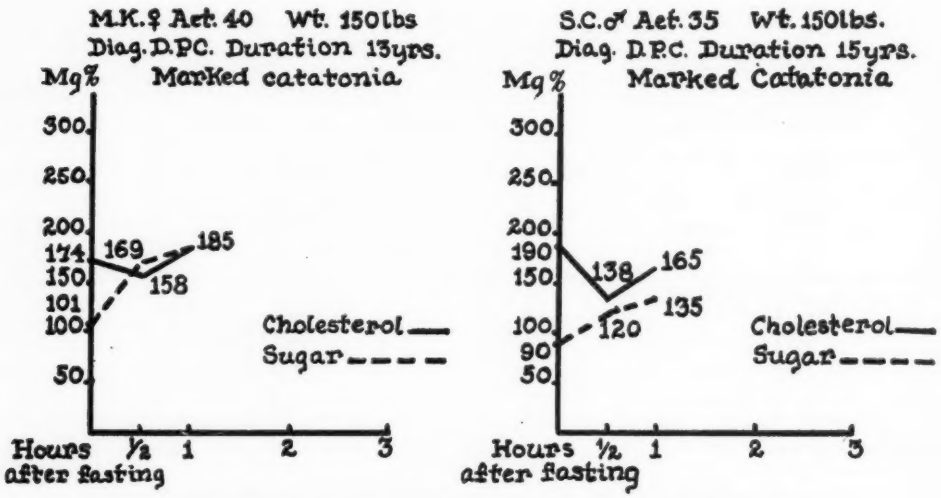

Fig. 3 Response of blood sugar and cholesterol to epinephrine HCl 1-1000 1mn for each 10lbs. body wt

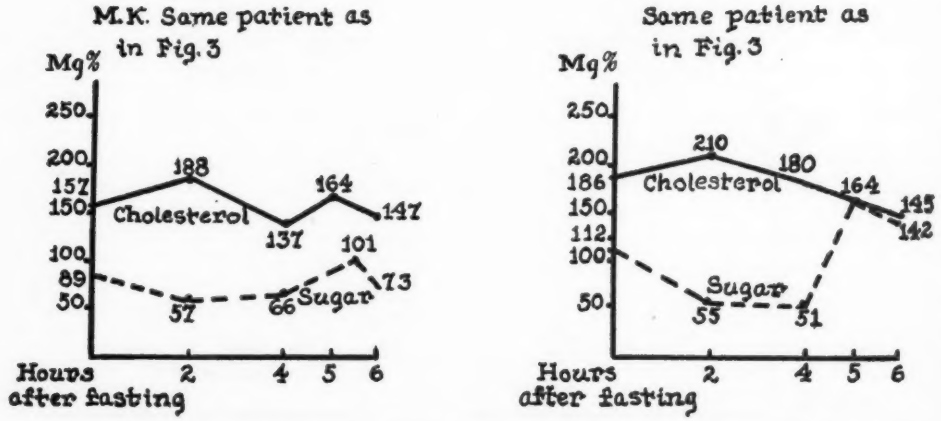

Fig. 4. Responses of blood sugar and blood cholesterol to 20 units of insulin — 100gms. glucose given at end of 4hrs.

may serve a practical purpose, since this is the patient whom the family wishes to care for at home.

Of the other patients, some would fall definitely into the manic depressive group with special factors of onset or special symptoms vitiating the prognosis. Excluding the patients drawn from our own chronic services, the patients selected for treatment had been in hospitals for a long period of time and, with few exceptions, had shown little or no improvement. The number treated is less than fifteen per cent of our current admission rate.

The following case, reported in detail, is one of apparent schizophrenia. The glucose test showed a direct shift of the sugar and cholesterol, whereas, the epinephrine response was active with inversion of the shift. This patient is at home on a trial visit. It is hoped that the improvement will be sustained and that the blood studies can be repeated.

CASE REPORT

The patient, a white woman, aged 22, single, was admitted July 3, 1937.

Both parents are living and well. No case of mental disease is known in the ancestry or collaterals.

The patient was born at full term, by a normal delivery. She is an only child and the mother was past 30 at the time of her birth. She had asthma as a child and had had one attack of pneumonia. She was subject to frequent colds with nasal discharge. Submucous resection was done in 1932; appendectomy in 1933. She started to school at 6 years of age, completed one year of college work and was in the second year of college when her mental health suffered a complete breakdown. This was in November, 1934.

During her second year of high school, the quality of the patient's school work underwent a notable change. Previously she had always made the highest marks in her class. Now her scholarship showed marked decline and she complained of inability to concentrate. She had been refused permission to join a club because of parental objections to dancing. This made her unhappy and she began avoiding her friends, whereas formerly she had been normally sociable with other children. She was sent to boarding school for the last two years of high school work. She seemed better satisfied at the boarding school, but did not regain her scholastic standing. The submucous operation on her nose caused her to lose some time in her last year of high school. The following year she attended a woman's college. In this year, too, she lost some time because of the appendectomy, but she completed the freshman year with one "condition." She returned to this college for the second year's work with reluctance and no enthusiasm. After six weeks she wrote her mother that she wanted to be a nurse and expressed the desire to enter the training school of Johns Hopkins Hospital. Her parents, alarmed at the tone of the letter, communicated with the college authorities, and these reported that the girl had left her dormitory to visit a friend in a neighboring city. Investigation disclosed that she had made her way, with much hardship and apparently in a confused mental condition, a considerable distance to the home of an aunt in another state. Here her parents joined her. For three weeks the patient and her parents remained at the aunt's home. The patient was restless, slept poorly, showed antagonisms and anger at being opposed and liked to lie on the floor and draw pictures in a childish manner. The restlessness and periods of excitement increased during the three weeks and it became necessary to give her sedatives to quiet her and produce sleep. She was then taken to a psychiatrist, who observed her for three days. He noted active hallucinations and diagnosed her case as dementia precox with the reservation that the hypnotic drug might be

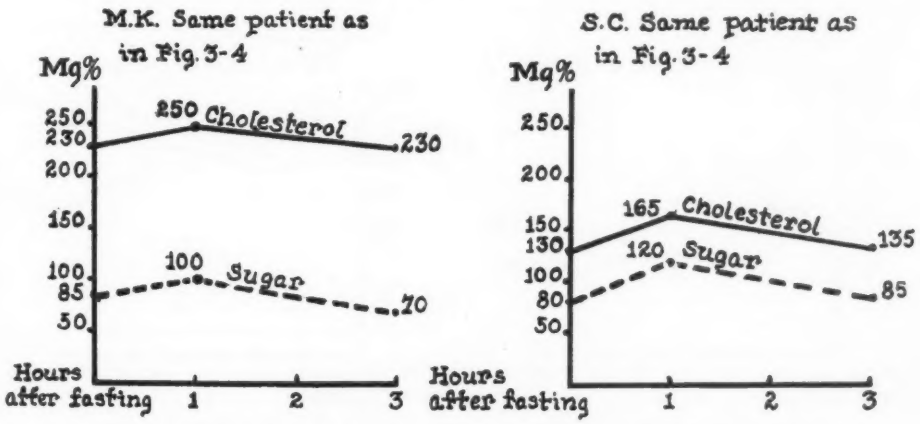

Fig. 5. Typical Schizophrenic responses of blood sugar and cholesterol following ingestion of 100gms. glucose.

partly responsible for the hallucinations. He advised sanitarium treatment and she was immediately taken to a large Eastern hospital.

After nine months' treatment at this hospital the patient showed marked improvement with good institutional adjustments and was allowed a trial visit with her parents. At the end of two months she had to be returned to the hospital, where she continued under treatment for an additional twenty months. She became increasingly disturbed during this period and was discharged unimproved with the diagnosis: schizophrenia, and prognosis poor.

The patient was a young woman of the agile, athletic type of body conformation, with slanting shoulders. Her posture was good; weight, 110 pounds; height, 5 feet 2 inches; temperature, 99.2° F.; pulse, 96; respiratory rate, 18; and blood pressure, 130/90. (She had been in dry pack *en route* to the hospital and had been given paraldehyde for sedation.) The skin was mooth and free from blemishes other than appendectomy and vaccination scars. The fine hair on the upper lip was pigmented and slightly increased in length, and fine, pigmented hair extended from the scalp down in front of the ears and on to the back of the neck and between the shoulder blades. Hair was unusually abundant on the arms and legs. The pubic hair ended in a horizontal line across the top. There were no evidences of organic defect, signs of distress nor areas of tenderness. The tendon reflexes were all slightly increased. The sensorium was apparently intact and there was no evidence of incoordination.

Report of Urinalysis.—The admission specimen was amber in color; specific gravity, 10.21; reaction, acid; albumin, trace; sugar, negative; acetone, 2 plus. The second day specimen was light yellow; specific gravity, 10.21; reaction, acid; albumin, negative; sugar, negative; acetone, 2 plus. Microscopic examination was negative. One and three hours after the glucose test meal, sugar was positive; acetone, negative.

Blood.—Red blood cells were 4,100,000; hemoglobin was 12.4 gram per cent. White blood cells were 9,700; differential count, neutrophils 78 per cent, eosinophils 1 per cent, small lymphocytes 18 per cent, myelocytes 3 per cent. Sedimentation test: 0.7 mm. per minute. Pack: 38.5 mm. per cent. Blood Wassermann negative. The results in the blood sugar and blood cholesterol tests are shown in *Fig. 8*. On the eighteenth day of treatment, four hours after a dose of 90 units of insulin, the blood sugar was 39.2 mg. per cent and the blood cholesterol was 125.7 mg. per cent. Sweat scraped from the skin at this time was negative for sugar and cholesterol.

Systematic questioning of the patient was not carried out, as this had been most thoroughly done during her previous hospitalization. Apparently, she was oriented as to time, place and persons and had no appreciable memory defects. She recalled clearly acquaintances in the hospital where she was first treated.

The patient spoke definitely and often of being married to a physician in the first hospital. At other times she spoke more vaguely of being engaged to marry him. She was given to gazing into space and smiling or laughing out in a manner to suggest reveries approaching hallucinations. There were one or two episodes of talking noisily out of the window at night.

She was listless most of the time when undisturbed; defiant and assaultive when disturbed. She was resistive to venipunctures and had to be held by nurses when blood specimens were obtained. She often had to be held when hypodermics were given. She had also a few spontaneous outbursts, once smashing a drinking glass against a mirror, again smashing a vase containing flowers, and once screaming and kicking in a childish manner on having to go back to her room for bed after one of the bi-weekly parties.

Treatment, with Comments on Reactions and Afternoon Responses.—Hypoglycemic treatment was begun on the third day after admission. The initial dose, administered at 6:00 a. m., after a twelve hours' fast, was 25 units of U-100 insulin. It was given deep in the buttock with a one-inch twenty-four-gauge needle. The patient resumed her sleep for two hours and awakened apparently recovered from the insulin and fussed mildly for food, but with encouragement she continued with-

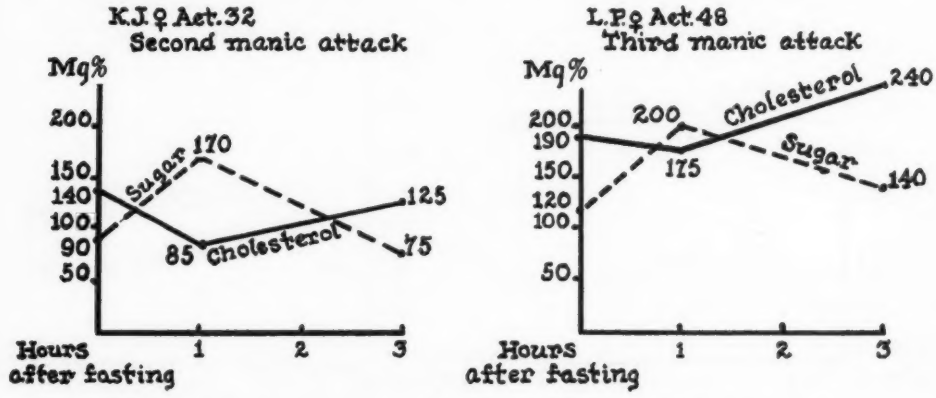

Fig. 6 Manic responses of blood sugar and cholesterol following ingestion of 100 gms. glucose.

out food for four hours, after which she was given 4 ounces of Karo corn syrup in orange juice and allowed to remain in bed for another hour. She then took a bath and dressed, remaining in her room until after dinner at 1:00 p. m. During the afternoon she walked about the grounds with her nurse, returning to her room for supper. She also acquired a design upon which she did some embroidery. The second day she was given 30 units of insulin in the same manner and at the same time, with the same reactions and response for the day, except that she did not work on her embroidery. The dosage of insulin was then increased 10 units daily for four days, after which the first rest day was given. She resumed her embroidery on the third day and also occupied herself with pencil and paper, designing figures that were executed with almost mechanical skill. On the ninth day her shock dose was reached and she required tube feeding at the end of four hours for release from the effects of the 90-unit dose of insulin. This dose level was held for three more doses, after which the second rest day was given. The following day there were some convulsive twitchings of the muscles and the glucose was administered by nasal tube and when the convulsiveness became more severe 20 c. c. of a 50 per

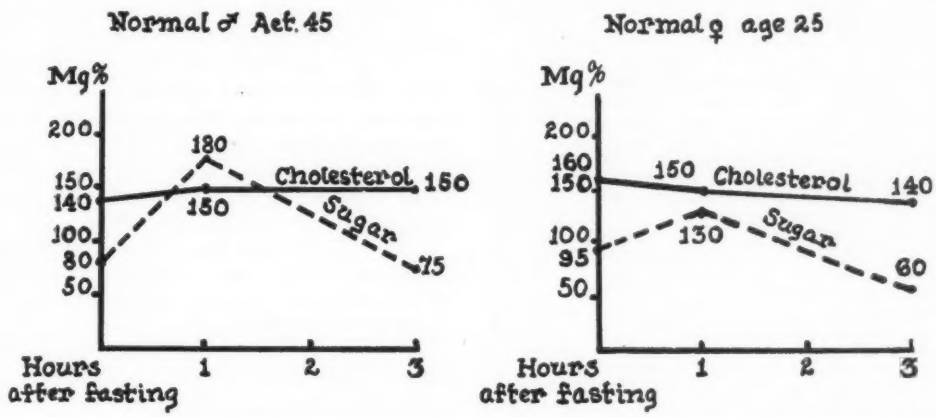

Fig. 7 Normal responses of blood sugar and cholesterol following ingestion of 100 gms. glucose.

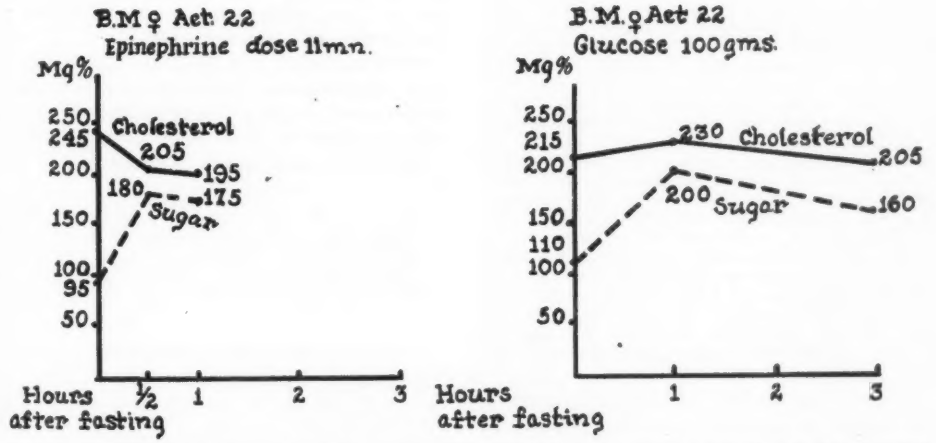

Fig. 8 (case reported) Responses of blood sugar and cholesterol following 11mn. dose of epinephrine HCl 1-1000, and following ingestion of 100 gms. glucose.

cent solution of glucose was given intravenously. Another rest day was allowed and the 90-unit dose was resumed on the following day. Again the patient reacted with convulsive twitching of the muscles, but the tube feeding was given more promptly and the intravenous administration was not necessary. The 90-unit dose was continued, but muscular twitchings caused the reactions to be terminated between the second and third hour each day. After the fourth weekly rest day, decreasing doses were given and two and three-day rest periods were allowed over the week ends. Satisfactory somnolent reactions continued, with only occasional muscular twitchings, until the dosage was back to 20 units on the thirty-ninth and fortieth days of treatment.

During the course of the treatment thus far there had been general improvement in appearance, alertness and initiative. The patient was friendly with the nurses and other patients most of the time, but there were discouraging lapses. At the end of the three-day rest period she became excited, again talking about being married and insisting that she be allowed to go back to her former hospital to live as the wife of one of the physicians; spoke of hating her parents and of everything in the world's being ugly and mean. On the forty-fourth day the insulin therapy was resumed in the usual manner, 30 units of U-100 insulin being given at 6:00 a. m. The patient had to be held by the nurses and continued angry and assaultive, refusing to stay in bed or to allow the nurse to stay in her room. During the afternoon she was able to go for her walk as usual and was in fairly good mood. As the dosage was increased in 5-unit steps she continued resistive to taking the hypodermic injection and had to be restrained with a sleeve apron to keep her in bed. There were both initial and secondary periods of excitement, during which she always protested that she was well, had never been ill and only wanted to live her own life.

Full shock dosage was reached at 75 units on the sixty-sixth day, and with four days of full shock she seemed completely herself, speaking with good insight in reference to the onset of the illness and of frequent past episodes of excitement. She spoke of wanting to go home to live with her parents and see if she could not get well enough to resume her college work. A visit from her parents on the seventy-fourth day and after a three-day rest period was received with an enthusiasm that had been foreign to her on previous visits, but she seemed over-anxious to go home. She seemed embarrassed when I tried to make her talk of recently passed episodes. But she allowed her parents to bid her goodbye on the grounds, and after this went to her supper and to her room in a good state of composure. At my evening visit she talked calmly about her condition and agreed to come back to the hospital for more treatment if she were allowed to go home and did not get along as well as could be wished. The next morning it was decided to give her a trial at home. She was discharged to her parents on the seventy-fifth day after insulin treatment had been instituted.

From the studies and observations of others than myself and associates, this case would represent a most unfavorable prognosis.

CONCLUSIONS

The following observations have been made in a series of twenty-nine patients with psychoses of long standing who received insulin treatment by Sakel's method:

(1) Of twenty-two patients who received systematic insulin shock treatment, sixteen have shown remarkable remissions of active psychotic symptoms, five did not respond favorably, and in one case the active symptoms returned after an initial remission.

(2) In seven patients who received modified insulin shock treatment the results suggest that even in such modified form the treatment may prove valuable in aborting episodes of violence in chronic periodically disturbed patients (three cases) or in improving appetite and nutrition. Two patients in this subgroup have given promise of improvement justifying systematic treatment, which they are now receiving.

(3) The most favorable responses to the hypoglycemic therapy were seen in intensely disturbed acute cases, whether considered manic or catatonic excitements.

(4) Recurrence in one case warns against hasty judgment on ultimate results.

(5) No deleterious effects from the insulin shock treatment in this series of patients have been observed within the eleven months in which it has been used.

(6) Biochemical responses of the blood sugar are offered as an aid in the study of initial responses for indications of safety before full shock treatment is undertaken.

(7) Concurrent cholesterol determinations after administration of epinephrine and glucose show a trend of shifts that promise to be of some value in prognosis or in biological grouping.

(8) A case is reported in detail.

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DISCUSSION (*Abstract*)

Dr. Charles S. Holbrook, New Orleans, La.—There is a tremendous amount of enthusiasm about the hypoglycemia treatment, in which I have fully shared. My experience with it has been encouraging.

We do not know what cases it should be used in. We should like to determine which types of mental disorder respond to it, whether it should be restricted to dementia precox or to certain types of precox;

whether some other treatment such as metrazol would give better results in certain cases. Blood chemical analyses before the patients are subjected to treatment, as blood sugar and cholesterol determinations or electro-encephalograms, may help us to determine which cases are apt to respond favorably. I believe the best results are not going to come out of research from large institutions. Unfortunately the nature of things makes it so that the cases in large institutions are usually rather well established. They have usually existed for a number of months or years before they are admitted. Results from insulin treatment seem to go hand in hand with the acuteness of the attack, and the cases that can be treated early, thinking of dementia precox primarily, certainly give the best results. In small hospitals and private work we shall probably be able to handle some cases better.

There is something else that Dr. Allen impressed upon me in his work. It is that some of the old cases, some of the chronic patients who have been on the back ward, as it were, institutionalized for many years, apparently very far dilapidated and a source of much trouble from a nursing point of view, in feeding, have responded to treatment, have gotten out of the catatonic states they have been in, have been more readily taken care of subsequently, have adjusted themselves more thoroughly to institutional life, though probably not recovering well enough to be considered as restored. Certain of these cases will certainly be benefited by insulin treatment. I am sure that we are critical about this in our viewpoint, though we feel much enthusiasm. I am afraid the enthusiasm we have may trip us up; still this work with hypoglycemia and insulin shock is certainly bringing about a tremendous urge for further investigation. For years the prognosis has been so bad and the outlook so dreary for these patients that I feel that we are in a new era as far as clinical investigation is concerned.

Dr. Lionel L. Cazenavette, New Orleans, La.—For a considerable number of years, especially during the past five years, I have been in direct contact with psychiatric cases of all types, especially since my association with the City Hospital for Mental Diseases. Dr. Allen is to be thanked for giving to the profession at large the benefit of his observations on 29 cases of psychosis of long standing which he has subjected to insulin therapy. These observations are of greater value because they were not confined to cases of dementia precox, but also included other types of mental disorder. It is gratifying to know that 16 out of 22 gave a favorable response with amelioration of psychotic symptoms. It should be noted also that in 7 cases of psychosis of long standing there was a modification of the condition after insulin treatment, and many have returned to a fairly normal condition, as far as being able to take care of themselves.

The number of admissions at the City Hospital for Mental Diseases, choosing the years 1934, 1935 and 1936 arbitrarily, was 1,153 cases, and roughly 25 and 30 per cent of these were of the schizophrenic type. Many cases are kept in our hospital for from six weeks to three months and then are sent to the State Hospital for continuation of treatment of their condition. The treatment received at the City Hospital has been helpful to them because a large percentage, after remaining a few months at the State Hospital, are sent home as fairly recovered, or rather with a fair remission of their reactions. In insulin treatment we do not know how necessary it is to induce coma or a severe reaction. Some patients, I understand, respond very severely to a small dose of insulin and others take a very large dose without much reaction. Whether it is the hypoglycemic state which helps the patients, we do not know. Another treatment consists of the administration of metrazol, which also gives a series of shocks. After repeated shocks of this type they respond fairly well, as far as their psychotic conditions are concerned. We should be careful in using this form of therapy, because we do not know enough about it. It is certainly not a specific, as everybody seems to agree, and in the schizophrenic reaction it is well to administer it only in well chosen cases.

Dr. T. A. Watters, New Orleans, La.—One of the things that impressed me this summer when I was in Vienna, at which time I saw Dr. Sakel's work, was this: his extreme conservatism of attitude towards his work and his tinge of skepticism in regard to it. He impressed me as a first class scientist and he was conservative. He said very definitely, however, that the cases which had convulsions gave the best results.

My co-workers and I at Tulane have begun the metrazol treatment. We are going to try to keep it within the bounds of reason.

Dr. Mason Smith, Tampa, Fla.—In December of 1936, I wished to administer insulin therapy, and acquired my first information from Dr. Allen over a long-distance telephone where the static was very bad. I have since that time become probably over-enthusiastic and have administered insulin to a large group of psychopathic patients who have entered the Tampa Municipal Hospital, probably over 100, of every type. Of the types that have yielded the most favorable results, the schizophrenic is the most numerous, with the hysterical and psychoneurotics next. The treatment has been used in maniacs and anxiety states, in the treatment of morphine addicts, in alcoholics, in involutional melancholics, and in all types of mental disease.

Twenty-six schizophrenics have been subjected to prolonged therapy. Of the 26 we have had 13 which we term complete remissions. Two of these relapsed after ten days out of the hospital because, we thought, the therapy had not been carried far enough. They were brought in for further therapy, were discharged last June and the remission has been maintained. Of the 13 we have had no follow-up on 2: one disappeared in Cuba, another somewhere else. Two are now headed for discharge. We have treated two cases which were brought over from the state hospital, of three years' standing. In one of these complete remission was attained and the other was a total failure. Of the whole group, there have been only 4 total failures, 7 recoveries, and 2 social recoveries, where a commitment was not necessary. In that community there are many psychiatric patients, there is a Latin population with bad sanitation in some of the quarters, and the state hospital has been so overcrowded that there has been no opportunity for admission of patients as they break down with psychoses, so the jails and hospitals have been filled. This therapy has to some extent solved the problem with the schizophrenics.

THE SYMPTOMATIC TREATMENT OF THE PARKINSONIAN SYNDROME WITH COBRA VENOM*

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and
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The venom of snakes has been used in medicine since early times. In the records of medieval Hebrew and Arabic medicine is found a treatise which deals with the use of certain poisonous snakes in the treatment of leprosy and cancer. Snake venom was given orally until modern times, whereas the parenteral administration of snake venom is an achievement of recent years.

Snake venom has been used empirically to a considerable extent within the last decade or two. Rattlesnake venom was employed in the treatment of epilepsy by Mays,[1] Fackenheim, Prevost, Jenkins and Pendleton,[2] Thom[3] and others. The venom of the moccasin has been used in the treatment of certain hemorrhagic diseases. Recently, the French authors, Calmette, Taguet and Monaelessor, Laignel-Lavastine and Korressios have reported beneficial results in the use of injections of cobra venom in patients suffering severe chronic pain, as a result of malignant disease. Very recently, Alexander Rottman[4] of Berlin has reported the beneficial use of cobra venom solution in the treatment of the pain and crises of tabes dorsalis.

The work of Macht[5 6 7 8] in a study of the physiological and pharmacological effects of cobra venom and its preparation has been a decided advancement. He states that his object was: (1) to study the general pharmacology and toxicology of cobra venom according to the latest technical methods; (2) to prepare and assay biologically a sterile solution of cobra venom for therapeutic use in human patients; (3) to carry out a carefully controlled clinical investigation in order to ascertain the action of cobra venom injections on patients affected with malignant tumors causing severe pains; and (4) to analyze the more intimate pharmacological action of cobra venom. From a therapeutic standpoint he divides snake venoms as follows: (1) the venoms of the (Crotalidae) rattlesnake which have been used chiefly in the treatment of epilepsy. This treatment, however, has been largely discontinued because of the rapid decomposition of the product, and the difficulties encountered in its preparation. (2) The moccasin (Ancistrodon) venoms, and Russell's viper venom, which it is believed, will promote coagulation of the blood. Its use has been recommended in the treatment of purpura and other types of hemorrhagic states. Moccasin venom is said to have no effect on true hemophilia, although some writers contend that Russell's viper venom is helpful in that condition. The evidence of the effectiveness of moccasin venom solution has not been proven by clinical investigation, and for that reason, its use has been largely discontinued. (3) The venom of the cobra, even in small doses, affects nerve cells and other nerve elements. This venom has been found useful in alleviating severe pain induced by advanced and malignant tumors, to such an extent that the preparation may be used as a substitute in some cases for narcotics and other analgesics.

Cobra venom is toxic to all animals above the hydra, exerting its action primarily upon the blood and nervous system. Its action on the blood is to alter the coagulability, so that the red blood corpuscles are dissolved with a tendency to extravasations and thrombosis. There is a marked reduction of the leukocytes, frequently to as low as 25 per cent of the normal number.

In man, following a toxic dose, there is an incubation period of about four hours and then the patient becomes drowsy. Thereafter, an ascending paralysis of the cord is noted, beginning with the legs, then the arms, the larynx and the tongue. The respiration becomes difficult and labored, often giving rise to asphyxial convulsions. This is due to a bulbar paralysis and the heart beats for some time after respiration ceases. A paralysis of the vasomotor center often occurs which produces a fall in blood pressure. The important constituent of cobra venom having a predilection for nerve tissue is a neurotoxin, the chemical composition of which is still unknown.

The preparation of cobra venom solution used in the intramuscular administration has to be carefully made, and there are two points that especially demand careful consideration. The venom solution must be furnished in such a state that it will be harmless, particularly with regard to bacterial infection, and in order to make it so, the solution of physiological sodium chloride must be sterilized by special methods. These

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methods are necessary because, although cobra venom is fortunately much more stable and resistive to heat than rattlesnake venom, it nevertheless deteriorates in potency when heated to more than 70° C. It has to be sterilized, not merely for freedom from ordinary aerobic bacteria, but also from anaerobic ones.

The cobra venom used in the preparation of the solution is not collected from cobras in this country. Dry scales, or the dry crystalline secretions, are obtained from both the Indian and the African cobra. The cobra venom solution which we used contains a small quantity of tri-cresol, the odor of which can be detected, and which probably is responsible for a slight sensory change (or slight amount of discomfort) in the extremity, immediately after the injection of the drug.

For obvious reasons, it is important to emphasize an accurate assay in the preparation of cobra venom for clinical use. The chemistry of cobra venom has not as yet been solved, and therefore the assay can only be made by biological standardization. The pharmaceutical manufacturer of the product used in the treatment of our cases employs the mouse unit as a standard. The unit is the quantity of cobra venom solution which will kill a mouse weighing 24 grams, within eighteen hours after intraperitoneal injection. This mouse unit has also been adopted by the French, German and other investigators. The solution used in our cases contains five mouse units to the cubic centimeter of salt solution. The lethal dosage of the venom in great dilution injected continuously is small, but no more poisonous than nicotine or aconitine hydrochloride. For therapeutic purposes, the effective dose is five mouse units given intramuscularly, but much larger doses have been administered without harmful effects.

There is not a great deal in the literature which is conclusive concerning the exact action of cobra venom on the central nervous system, but it is accepted that there is a neurotoxin which strikes the higher nerve centers of the brain. Macht has shown that cobra venom is not a local anesthetic, that it does not affect even the nerve fibres and nerve trunks in experimental animals, when applied locally; that doses of cobra venom injected intraperitoneally in mice act as an antagonist in cerebral convulsions caused by certain drugs; in other words, the cobra venom solution acts as an antagonist to the convulsant effect which follows the use of such drugs as camphorated oil, santonin, and others, which are generally regarded as affecting the higher nerve centers. [9] [13] It is thought that the cobra venom relieves pain in much the same way that morphine does, in its action on the cerebrum, but without exerting the narcotic effects of the drug.

The use of cobra venom solution in the treatment of the Parkinsonian syndrome was suggested for the reason that it has been proven acceptably that the intramuscular injections of this solution may relieve chronic pain; and in view of the fact that certain cases of paralysis agitans suffer with pain, it was decided to use this product in the hope of relieving this distressing symptom. It was found in certain cases of the Parkinsonian syndrome, that not only the pain was relieved, but certain other symptoms, such as increased spasticity and tremor, were also benefited.

Our interest was aroused because we felt that the methods of palliative treatment for the condition were not sufficient, and we were searching for a more efficacious procedure. The first case which we treated with cobra venom was one of rather long standing, which had progressed to a considerable spasticity, a marked disturbance of gait, and extensive tremors of all extremities. Our effort was discouraging in the beginning, for the reason that this case was not improved in the least; nevertheless, we decided to carry the experiment further. The second case was an earlier one, who had been under our observation for a period of several months, and who had shown some symptomatic improvement with the use of scopolamine. During the time that this patient was given the cobra venom solution, no other medicine was allowed, and he did as well or better than he had previously done on large doses of scopolamine.

The present group of cases to be reported consists of eighteen individuals with well developed signs and symptoms of the Parkinsonian syndrome. They exhibited the typical findings of muscular rigidity, non-intention tremors, masked facies, pains, and altered gait. In most instances the onset followed some acute infectious process such as typhoid fever, pneumonia, influenza or grippe, which produced an encephalitis. Some of the individuals failed to recall such an illness, yet it was difficult to believe that arteriosclerosis was the causative factor in many. The duration of the disorder ranged from three years to twenty years, and was progressive in character. The ages of this group of patients varied from 21 years to 69 years, at onset, with an average age of 45 years.

The method of treatment followed in each case

was to give the patient 0.5 c.c. of cobra venom intramuscularly the first day, and then 1 c.c. every other day for ten doses. If no subjective improvement was effected by this number of doses, the treatment was discontinued. After the completion of ten injections, a complete neurologic examination was made, and was compared with the examination made at the beginning of treatment. During the course of treatment all other medication was discontinued, or practically so, which caused an increase in the discomfort of the patients at first, as all of these patients were taking rather large doses of stamonium or scopolamine, which had made them relatively comfortable.

Due to the fact that patients with Parkinson's disease could rapidly withdraw their scopolamine, stramonium, or other anti-spasmodic drugs after a few doses of the venom, and that the interval between the injection of the cobra venom solution was lengthened with no increase of the patient's symptoms, it was believed that there was some cumulative effect of the venom. One very intelligent patient made just that observation and expressed it spontaneously. In all of them who showed improvement, we were able to lengthen the interval between doses with no increase in their symptoms. We have discounted as much as possible, the likelihood of any psychic effect during and following the treatment.

The most outstanding effect of the administration of cobra venom was the relief of pain and this occurred in all cases which presented that symptom. Usually the pains were relieved after about the fourth or fifth injection was given, and this has lasted until the present time. In 67 per cent of the cases there was marked subjective improvement; but little objective change was noted. These individuals stated that there seemed to be less muscular rigidity and they were able to perform tasks which were impossible before treatment. There was noted an improvement in their attitudes, in that they were encouraged, more cheerful, and decidedly less nervous. Most of these patients were able to do without other medicines or they materially reduced the amount following the injections, which may be interpreted as improvement.

In 33 per cent of the cases treated there was no improvement, either subjective or objective. These individuals were older than the average, and the duration of the disease was much longer. Only one patient discontinued treatment after one injection, stating that it made him much worse, whereas, the other patients completed ten injections, and in five cases another series of ten injections was given, but with little change in the symptoms.

A patient, not included in this series of cases, was diagnosed as having encephalitis about ten years previously, who later developed a typical picture of multiple sclerosis, with considerable pain as a symptom. She was given ten intramuscular injections of cobra venom, with no relief whatever of her pain or other symptoms.

SUMMARY

It is our opinion that cobra venom solution is a valuable aid in the symptomatic treatment of the Parkinsonian syndrome; that it has an accumulative effect when given in small doses intramuscularly; and that it can be partially substituted for drug therapy in certain cases of Parkinson's disease. In none of our cases did the use of cobra venom solution effect any material change in the objective symptoms of the disease, and certainly the tremor was not affected by its use.

This report is a preliminary one, and we plan, at a later date, to give a more detailed report of our results in a larger series of cases.

Acknowledgment is hereby given to the Department of Neuropsychiatry of the Medical College of Virginia for supplying some of the material for this series of cases, and to Doctor David I. Macht, Director of the Research Department for Pharmacology of Hynson, Westcott and Dunning, Baltimore, Maryland, for supplying the cobra venom solution used in the treatment of a number of these patients.

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Professional Building

DISCUSSION (*Abstract*)

Dr. Frank H. Redwood, Norfolk, Va.—In opening the discussion I should like to quote the conclusions from a recent article by Dr. Macht. "There is no sharp distinction between drugs and poisons. All drugs worthy of the name may become poisons when injudiciously employed. Conversely, almost all poisons, or at least a very large number, may be employed as valuable medicines. Snake venom is no exception. Many a virulent poison has proven to be a useful therapeutic agent and the number of serpents which, pharmacologically speaking, have no charm, is rapidly diminishing."

Snakes have been used for treatment even in the Dark Ages, but not until recent years has snake venom been employed therapeutically on any rational and scientific basis. The venoms chiefly in use are moccasin, for the control of certain hemorrhagic states; rattlesnake in the treatment of epilepsy, which has not been very successful, and cobra venom for the control of intractable pain accompanying malignant tumors.

It would seem that there is another rather definite use of cobra venom in treatment. Dr. Gayle rightly has not drawn any conclusions and has only given his observations on a series of cases. It is interesting to note that his cases showing symptomatic improvement have done so on less frequent doses than when treatment was begun, which shows the possible cumulative action of the venom. This has also been brought out by Macht and others in treating the pain accompanying malignant disease. Macht has also shown that the action of cobra venom on the pain areas of the cerebrum is not unlike that of morphine, but the effect lasts much longer.

Feldberg and Kellaway report that large doses of cobra venom in the vein cause an immediate fall in systolic blood pressure and a marked distention of the right heart while the left heart is empty. This they think is due to pulmonary constriction. They further say that the initial fall of blood pressure is due to the liberation of histamine brought about by the introduction of cobra venom directly into the blood stream. I am wondering if it is possible that histamine could be liberated by the intramuscular injections of venom and might not this have something to do with the symptomatic improvement in Dr. Gayle's cases. I should also like to ask if he has observed any lowering of systolic blood pressure after intramuscular injection of venom.

If anything has been found which is more efficacious than those drugs in common use for the symptomatic treatment of Parkinson's disease I would say that much has been done.

Dr. T. A. Watters, New Orleans, La.—The snake has always had an interesting place in the folk treatment of various disorders. In Scotland the Highlanders used to put live snakes in a bottle of water for a period of time, then drink the concoction to effect helpful results in epilepsy. In Austria a snake's head was put in rum and the potion imbibed for the same disorder. The Tyroleans took the "gall" of two adders. It is not unreasonable to assume that the venom may have been the active principle at work in these primitive forms of treatment.

In modern times snake venom has been used in epilepsy, and from all accounts it seems to have been the first neuropsychiatric condition where the snake was again called upon for help. Mays advocated its use, and likened its effects to that of the cyanides. Other observers, however, have not found this to be true, because many patients experienced stimulation rather than depression; cyanides reputedly cause depression. Jenkins and Pendleton concluded that venom did not decrease, but rather increased the convulsions. Thom likewise became discouraged with regard to the use of venom in the epilepsies. In eleven cases, six showed no improvement, four became worse, one improved, but this case Thom considered to be hystero-epilepsy, and felt that in the final analysis psychotherapy may have played the larger part.

As time has passed venom has been reported effective in several other neuropsychiatric conditions: neuralgias, especially sciatica, trigeminal neuralgia, and tabes dorsalis, where there were severe crises. One notices immediately that those conditions where it has been used are those which feature pain as a prominent symptom.

Its pharmacology deserves some consideration. Macht probably has done more work on venom than anyone else in this country, but with the results at hand, it is fair to say that his findings are not beyond the range of contention. It is not a local analgesic, for sensory nerve endings, as shown by experiments on frogs' skin, and the wheal method in guinea-pigs. Direct application to nerve fibers and trunks of frogs and cats produced no anesthetic effects. When quantities are added to Locke's solution with surviving smooth muscle preparations of the bladder or the intestine, they do not readily paralyze the sympathetic or parasympathetic nerve endings, because these endings remain active to epinephrine, pilocarpine and atropine. It is Macht's belief that the pain is allayed purely through central action.

The same observer made psychological studies with animals and mazes, and his conclusion was that venom in small doses produced stimulation, whereas larger doses produced depression of central and neuromuscular responses.

Lethal effects are thought to be reached through changes produced in vital regions of the medulla. Venom seems to retard oxidation, incorporates itself in the brain tissue in large quantities and remains longer than does morphine; hence its more prolonged effects upon pain. Drs. Gayle and Williams show another interesting feature, and that is the cumulative effects.

Kelloway, who has done work on Australian snakes and reported his results in British journals, believes that the lethal effects of the more potent venoms are the results of paralysis of respiration through effects upon the peripheral nerves and are not central at all. The effects on smooth muscle he likened to those of an anaphylactic response in sensitive plain muscle. Several French workers agree with his views on the matter. Other pharmacologists believe the venom works in a way that is analogous to the curare group, such as arrowroot, sparteine, coniine. In the face of the divergences of opinion on the pharmacodynamics, however, we are given the assurance clinically that good effects accrue in the Parkinsonian states.

Drs. Gayle and Williams have made a valuable contribution and are very conservative and fair in their deductions, taking fully into account the fact that some cases will show improvement with indirect (physical therapy) or direct suggestion.

While on the staff at the Spring Grove State Hospital in Maryland, I had occasion to try tincture of gelsemium on a group of about ten cases of Parkinsonism, all of which were the results of chronic encephalitis. The doses ranged from five to ten minims, three times a day,

of a standard tincture. Very good results followed in about seven or eight of the cases. My conclusion was that it was a drug that deserved consideration in such cases. Therefore, in our armamentarium of drugs for the symptomatic treatment of Parkinsonian states we have: tincture of stramonium, tincture of belladonna, tincture of gselsemium, hyoscine hydrobromide, benzedrine, ephedrine, and cobra venom. These are all valuable drugs for symptomatic treatment, and by an increase in their number we have more opportunities for interchange and substitution when tolerance has been reached in any case.

In the final analysis, however, we must not forget that we do not treat sick hearts, sick basal ganglia, sick corpora luysii, or sick nervous systems *per se*, but rather we treat sick human beings, sick he's and she's who have as part of their physical organization these respective parts. By effecting environmental changes, better personal relationships and a better adjustment to work, play and hope, a better philosophy of the present and future, with adequate use of the material of memory, the symptomatic treatment will become more effective.

HERPES ZOSTER AND CHICKEN POX*

By CAREY C. BARRETT, M.D.
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I wish to discuss the relationship between herpes zoster and chicken pox. The subject is not of much practical value, but it is related to the study of virus diseases in general, which are attracting more and more attention. The literature on herpes zoster and chicken pox is voluminous. Most of the articles have appeared in the British and French literature. Cowern[26] could find but seventeen cases reported in the United States up to March, 1935. The subject has not been presented previously before the Section on Dermatology and Syphilology of the Southern Medical Association.

Several years ago I saw a 12-year-old white boy with a typical herpes zoster involving a group of the intercostal nerves on the left side. He was living with his sister, who was married and had five children of her own; twin babies, a little less than a year old, and three other children. On the sixteenth day of his eruption both of the twins developed chicken pox. The older children, as well as the patient with herpes zoster, had all had chicken pox before the twins were born. This large family lived in one of those cozy three-room shacks. The twins had been out of the house very little, and there were no known cases of chicken pox in the neighborhood at the time.

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About a year later I saw a white man, 38 years of age, with a very severe herpes zoster involving the right facial nerve. In addition to the eruption on the face, there were clusters of vesicles on the buccal mucosa and on the right half of the tongue. He had paresis of the facial muscles on the right side, some of which persists to date. This man had lived in Lexington but one month. His family consisted of a wife, and two children, aged 2½ and 4 years, respectively. The family had no friends in the city and the children had attended no public gatherings. On the seventeenth day of this patient's eruption he reported that both children had a skin eruption. On examination they were found to have chicken pox.

Von Bokay,[1] in 1892, first called attention to the development of chicken pox following contact with cases of herpes zoster. He believed that there was a causal relationship between the two diseases and has held this view from the time of his original publication to his most recent one[2] in 1928. In spite of the universally infectious nature of chicken pox and the possibility of accidental coincident infection, many cases on record leave no doubt as to the likelihood of herpes zoster's giving rise to chicken pox at certain times.

Most of the recorded cases of herpes zoster that have been followed by chicken pox in contacts have occurred in adults. The contacts that developed chicken pox were for the most part children in whom the disease appeared after an interval of fourteen to twenty days; the usual incubation period for chicken pox. There are many such examples in the cases reported. Netter[3] has collected reports of almost two hundred cases in a period of twenty years, appearing in France alone. There are probably forty to fifty such cases reported in the British literature. Only about twenty cases have been reported in this country and eight of them by one writer.[26] Most of the cases are like the two which I am reporting, that is, herpes zoster followed by chicken pox in contacts. Some of the reports contain points of particular interest.

Elliott[4] noted that of nine occasions when herpes zoster developed in a hospital ward, five were followed by chicken pox. Robertson,[5] Smith,[6] and others have made similar observations. There are a number of cases recorded in which children who had not had chicken pox developed herpes zoster which was followed by chicken pox in contacts, but the patients who had the herpes zoster did not develop chicken pox. They apparently acquired immunity to chicken pox from their attacks of herpes zoster.

Herpes zoster has also been reported as appearing in persons who had been in contact with cases of chicken pox, but this is rather rare. There are about seven times as many cases reported of herpes zoster followed by chicken pox as of chicken pox followed by herpes zoster.[27] In some instances there were further cases of chicken pox appearing in fourteen to twenty days after the case of herpes zoster appeared. Touraine, Hesse and Gole[7] report the case of a school teacher who developed herpes zoster after being exposed to cases of chicken pox in the school room. She was quarantined at home with her two children. Seventeen days after her first contact with her children they both developed chicken pox. While her children were convalescing from chicken pox one of them came in contact with an adult who lived in another part of the house. Seventeen days later this woman developed herpes zoster. This is the most striking case report that I have discovered.

Very few cases have been reported in which herpes zoster was followed by herpes zoster.

There are a number of cases of herpes zoster reported in which there was also a generalized eruption indistinguishable from chicken pox. These cases have been called herpes zoster generalizatus or herpes zoster and chicken pox combined, according to the bias of the reporter.

Microscopically the skin lesions of the two diseases are quite similar.

IMMUNOLOGIC RELATIONS

There has been considerable experimental work in recent years on the relationship of these two diseases, and some of the work also includes herpes simplex. Frei[8] introduced a complement-fixation test using blood serum from cases of herpes zoster and chicken pox vesicle fluid. Netter and Urbain[9] used this test and reported a positive reaction in over 90 per cent of cases of herpes zoster and chicken pox. Brain[10] has been able to confirm this work. This does not, of course, prove that the two diseases are due to the same virus. It may be the expression of a group reaction between two closely related kinds of virus. If these two diseases were followed by reciprocal immunity these results would carry more weight, but this is not true. Chicken pox does not protect against zoster nor zoster against chicken pox.

Amies,[11] following the work of Paschen, has succeeded in centrifuging and washing the elementary bodies in chicken pox vesicle fluid and then agglutinating them with blood serum from patients who had had chicken pox. He tried the same procedure with the elementary bodies in zoster vesicle fluid with the same success. He then tried cross agglutination with zoster bodies and chicken pox serum and *vice versa*. These tests were also positive, although in a somewhat lower titer.

Lipschultz and Kundratitz[12] inoculated children under five years of age with fluid from zoster lesions. Some of them developed a local reaction in 9 to 15 days. Those children who had had chicken pox could not be successfully inoculated with herpes zoster fluid. Ten children who were successfully inoculated were exposed to chicken pox and only five of them contracted the disease. Lauda and Silberstein,[13] however, could not confirm this work. Bruusgaard,[14] on the other hand, has recently confirmed these experiments. Fresh vesicle serum from a case of herpes zoster was inoculated into the arm of a two-year old child. Nine days later vesicles appeared. Fluid from these vesicles was reinoculated into two other children, one of whom developed a local vesicular reaction. After fourteen days, vesicles in crops appeared on the trunk, face, and scalp, accompanied by fever. The rash had the appearance of chicken pox. He was able to repeat these experiments on five occasions with five successive cases of herpes zoster, one of which had followed the administration of arsenic.

This, then, is a brief review of the clinical and experimental evidence in favor of a single etiologic factor as the cause of these two diseases. There are, however, numerous clinical observations that do not support this view:

(1) Herpes zoster is a localized disease seldom accompanied by fever. Chicken pox is a generalized eruption associated with fever.

(2) Herpes zoster is painful. Chicken pox is not.

(3) Herpes zoster is not contagious. Chicken pox is highly contagious.

(4) Herpes zoster is often accompanied by a regional adenopathy.

(5) A leukopenia with a relative mononucleosis is the rule in chicken pox, but not in herpes zoster.

(6) The spinal fluid in herpes zoster shows a lymphocytosis. The spinal fluid in chicken pox is normal. However, those in favor of a single cause for the two diseases point out that encephalitis has been known to occur in chicken pox.

(7) Herpes zoster affects adults chiefly and chicken pox is a disease of childhood. It has

been argued that herpes zoster appears chiefly in adults because their chicken pox immunity has diminished with age, but this argument does not stand up because if this were true one would expect to see an occasional recurrent attack of chicken pox, which is extremely rare.

(8) Herpes zoster gives almost complete immunity against another attack of herpes zoster, and chicken pox immunity is also permanent except in very rare instances.

(9) Herpes zoster does not give immunity to chicken pox; nor does chicken pox give immunity to herpes zoster. In all probability most cases of herpes zoster are seen in persons who have previously had chicken pox. Dietl[15] cites two instances in which children who had previously had chicken pox developed herpes zoster. Von Barabas[16] reports two patients with zoster, both of whom developed chicken pox eight and nine months later. Berinsohn[17] reports the case of a boy who had zoster and six weeks later had a typical chicken pox. Wilson, Mitchener and Little[18] report a case of chicken pox in which zoster appeared six weeks later.

(10) The majority of cases of herpes zoster are not followed by chicken pox in contacts. Comby[19] thinks that all such cases are a mere coincidence. Cantor,[20] who was the physician for twenty years on Christmas Island with a population of about 1,500, states that herpes zoster was frequently seen, but chicken pox was unknown. Storen,[21] in an isolated Norwegian village, made the same observation. Oppenheim[22] has for years placed all cases of zoster in a children's ward, but has never seen a case of chicken pox appear in the contacts.

(11) Chicken pox has a constant seasonal variation, but the number of cases varies little from year to year; whereas zoster seems to occur in small epidemics at variable intervals and in no relation to the incidence of chicken pox, although several authors have attempted to show that epidemics of the two diseases roughly coincide (compare Rivers and Eldridge[23]).

(12) Head and Campbell,[24] in 1900, in a widely quoted article on herpes zoster, point out that certain cases are due to the administration of definite chemicals, notably arsenic, bismuth, and carbon monoxide, and other cases are due to injury or disease of the spine or central nervous system, such as trauma, tabes dorsalis, Pott's disease of the spine, syringomyelia, and metastatic carcinoma. I have under observation now a patient with a tumor of the posterior lobe of the pituitary gland, who developed herpes zoster involving the right supra-orbital nerve.

(13) A number of cases of herpes zoster have been reported in which there was also a generalized chicken pox-like eruption over the entire body, which appeared at the same time or shortly after the zoster eruption appeared. These generalized lesions did not have a nerve distribution, they were not accompanied by pain or neuralgia, they were sometimes ushered in by fever as in the ordinary chicken pox, whereas the usual case of zoster is fever-free. They sometimes dried up and disappeared independently of the course of the zoster lesions. These clinical points have been offered as evidence that the individual can have the two diseases at the same time as a coincidence and therefore they must be due to different causes. Those who believe in the common origin of the two diseases call such cases herpes zoster with generalized or aberrant vesicles. It is well known that many cases of zoster are accompanied by a few aberrant vesicles widely scattered over the body. Those who believe in the common origin of the two diseases rightly point to the fact that in all such cases with a marked generalized eruption the zoster appeared first and the generalized eruption later, whereas if it were simply a coincidental infection with two diseases there would be an equal number of cases in which the generalized eruption would be the first to appear. Secondly, many of the reported cases had previously had chicken pox which we know gives permanent immunity against a second attack. Thirdly, most of the reported cases of this type have been in men of middle age or past, who were grossly undernourished and below par physically and in whom the herpes zoster was particularly severe.

THEORIES

There are, then, two main opinions in regard to these two diseases: the first is that they are caused by the same virus, and the second is exactly the opposite, that they are caused by distinct and separate viruses. Netter is the champion of the first view and Comby of the second. Other authors have suggested other theories:

(1) Some, but not all, cases of herpes zoster are caused by the virus of chicken pox, other cases being due to other causes.

(2) The virus that causes herpes zoster lies dormant in the central nervous system and causes the clinical picture of zoster only when injury, or disease, or intoxication gives it a site of lowered resistance in which to localize.

(3) Whether or not the patient develops herpes zoster depends on the portal of entry of the virus. If it gains access to the nervous system by way of the nasal tract or elsewhere the patient develops herpes zoster; if it gains entrance to the body through some other portal, which is not clear, the patient develops chicken pox.

CONCLUSIONS

Roxburgh's[25] conclusions and comments are worth quoting:

"On a balance of evidence it seems certain that some cases of zoster are due to the same virus as chicken pox. This applies not only to spontaneous zoster, but also to zoster in patients taking arsenic, etc."

There are many questions which remain to be cleared up, such as:

Is herpes zoster a syndrome that may be due to various causes? If so, what proportion of all cases of zoster are caused by the chicken pox virus? The experiments of Kundratitz and of Bruusgaard suggest that all cases are so caused.

If these two diseases are due to the same virus, why does the virus sometimes cause zoster and sometimes chicken pox?

Why is chicken pox in zoster contacts much more common than zoster in chicken pox contacts?

What is the explanation of concurrent cases?

What is the explanation of the case in which, in a few weeks, in the same patient, zoster follows chicken pox or chicken pox follows zoster?

Bruusgaard, in spite of the striking results of his experiments, says:

"The problem will not be solved until we have demonstrated the virus, or viruses, that cause these diseases,"

and that, at present, seems difficult because of the lack of a suitable experimental animal.

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DISCUSSION (*Abstract*)

Dr. Seba L. Whitehead, Asheville, N. C.—That chicken pox and herpes zoster have a common infective agent has been a subject of controversy for years. There are numerous instances in medical literature of herpes zoster's being followed in healthy contacts after the incubation period characteristic of chicken pox, too many instances to be mere coincidence. There has been ample clinical confirmation of von Bokay's observation. In spite of this seemingly convincing relationship between the infective agents of the two diseases, some authorities cite arguments to show that there is absolutely no relationship between them. Herpes zoster is an acute infection with localization in the posterior horn cells.

To support the contention that these are diseases of different etiology, and that their appearance together is coincidental, are the following considerations. Chicken pox is a common eruptive fever of childhood, while herpes zoster is uncommon in children. Seasonal incidence is common in chicken pox and not in herpes. Chicken pox is very contagious and herpes zoster rarely so. Chicken pox can be transmitted from one person to another by inoculation with the vesicle fluid. Herpes zoster cannot be so transmitted. Neither disease will develop from the vesicle fluid of herpes. Chicken pox produces a permanent complete immunity against chicken pox, but not against herpes.

It is evident that much research, both clinical and serological, has yet to be carried out to bring a satisfactory conclusion to the confusion which exists to date regarding the relationship of these two diseases.

Dr. C. F. Lehmann, San Antonio, Tex.—Dr. Barrett may not have given us anything new regarding this moot question, but he has given us a very valuable presentation.

The best scientific work which corroborates the hypothesis is that of Lipschultz and Kundratitz and of Bruusgaard, who have produced experimental lesions from the serum of herpes zoster. Until we know more about the nature of the viruses, serological studies have to be taken with considerable caution. We know that a virus is a very labile agent and, judging from clinical studies, the antibodies against chicken pox and herpes zoster are very variable and probably just as labile as the virus. These facts, with the facts as mentioned by Dr. Barrett, that no suitable laboratory animal has been found, make laboratory confirmation of this problem very difficult indeed.

A comparable problem is that in connection with the association of herpes simplex and smallpox. The fact that vaccination with smallpox virus helps recurring herpes simplex is a much more positive evidence that there is a close relationship between these two viruses. If such a result could be gotten by vaccinating with herpes zoster serum to prevent chicken pox all of the

positive evidence mentioned in the paper would be more strongly substantiated.

In the last four years I have seen forty-four cases of herpes zoster. I will admit that no thorough epidemiological survey was made, but these cases were closely questioned and some of them were followed long enough to determine whether any of their contacts developed chicken pox, and I have not seen or heard of any chicken pox from these cases. A few of them were associated with very bad local infections, such as sinusitis or tonsillitis, and I am inclined to the opinion that herpes zoster may be due to a streptococcus rather than to a virus; although I am open to conviction and think that this study should be more closely followed.

SOME EVIDENCES OF TISSUE INTERDEPENDENCE DURING DEVELOPMENT*

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All students of morphology and of physiology have occasion to wonder at times concerning the factors responsible for the differentiation which produces a certain form and permits a particular function. The laws and theories of heredity tend to convince us that many individual characteristics are determined by a chromosomal arrangement set up within the zygote. The embryologist has been able to show that the manner in which this zygote behaves may be conditioned to a marked degree by what happens during subsequent growth. Many examples of this dependent differentiation are observed in the process of integration of parts toward the production of a so-called normal adult. In some vertebrates two eyes will not be produced without the proper development of the indifferent layer which lies, or comes to lie, between them;[1] the lens ectoderm may not perform its proper function in the absence of an optic cup;[2] the cells of the posterior root ganglia fail to become clumped segmentally unless the mesoderm of the region undergoes segmentation also.[3] Many examples of this sort could be given, but it is proposed to limit the discussion to one general field in investigation which has been selected because of a particular personal interest in it. Possibly it might be more profitable to discuss the epoch-making and Nobel-prize-winning discoveries of Spemann[4] and his students on the organizer, that all important bit of protoplasm, constituting the blastoporic lip of the amphibian, which, apparently by chemical means, initiates, induces and organizes tremendous unwonted activity in whatever ectoderm it may contact. Certainly no better demonstration of alteration of the prospective significance of cells can be found anywhere and it is difficult to suppress a feeling of guilt in deserting this phase of the subject for one less well known.

It has been said many times that discovery of the nature of the factors involved in growth and differentiation must be left to the chemist and to the physicist, but even though the embryologist cannot aspire to too much, he has amply demonstrated his ability to make some rather more than preliminary studies in the field. By causing minor interferences along the course of development of an organism, he can learn many things about the fundamental relationships between the component parts of that individual. Some of these findings are of particular concern to the pathologist who observes, in his material, evidence of cellular deficiencies, overgrowths and maladjustments for which there seems to be no ready explanation. It may appear to be a far cry from the mollusc and the amphibian to the human and from the seaside laboratory to the autopsy room of a large hospital, but in many respects the cells encountered in such varied places are, or have been, possessed of similar qualities. In all studies of development the cell is the entity under consideration, no matter what material or what technic may be employed. There are many evidences of extremely early segregation of organic materials even in the fertilized egg. As the organism develops, the power of the parts to form different structures is gradually restricted, but we know that the potencies of the cells are greater than their ordinary work (that is, prospective significance) even after considerable differentiation has taken place.

Studies on cell-lineage in the development of certain marine animals furnished the initial impetus to all the later work in experimental embryology. Using the eggs of worms, molluscs ascidians, and so on, Conklin, Lillie and a host of other workers found that even during the first few hours of development, the material destined to appear in certain cells producing definite parts of the body could be sharply demarcated and subsequently followed to their ultimate destinations. As a sequel to these studies it was found that alterations of the relationships between these materials, by shaking or centrifuging the eggs, gave remarkable results. In many cases the material thus displaced became rear-

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ranged in normal fashion; in others various types of monstrosities were produced. Conklin's[5] more recently published work on Amphioxus gives one of the best demonstrations of the results of this method. Inasmuch as many of the abnormal individuals occasionally seen in nature are caused by accidental upsets in normal processes of development, the method of study seemed promising. By artificially changing the conditions of development, by altering the relationships between parts of the animal body, the experimenter is able to produce some of the peculiar conditions which occasionally occur spontaneously.

It is of course obvious that most of the experimental work of this kind must be done on members of the lower animal groups. It is unnecessary, however, to depend entirely upon the invertebrates as many of the vertebrates furnish excellent material. It was known to Bonnet and to Spallanzani, and possibly to others before them, that the legs of salamanders, when cut off, were replaced by the process of regeneration. Many experiments of this sort were made long before Roux, Pflüger and Driesch discovered that manipulation of the eggs of the frog sometimes resulted in abnormal development. Great advances in our understanding of the potentialities of tissues for growth and for regulation have been, and still are being, made by similar methods.

The next step, using that kind of experimental material, was initiated by Born's[6] discovery that parts of these young embryos could be transplanted, either to another individual, or to another region of the same individual. Born's original experiments consisted of cutting frog embryos in various ways and then uniting whole embryos or fragments in various positions. Harrison's[7] demonstration of the fact that anterior and posterior halves of two different species could be healed together and that a chimaera so produced could be reared through metamorphosis, gives an idea of the hardiness of the material and of the operative possibilities.

The methods of operating upon embryos were brought to America by Harrison, who used and developed them to a high degree in connection with his studies on the development of the neuroblast and the neurilemma sheath. For his investigations upon limb asymmetry a native salamander, Amblystoma punctatum, was chosen as the experimental animal. The eggs are fairly large, the embryos grow rapidly and are fairly resistant. For the work on the fore-limb, the salamander is better than the frog because, in the latter, this appendage is covered by the operculum throughout nearly all of its early development. Most of the work on the limb has been done on embryos in the tail-bud stage (*Fig. 1*). At this period of development the animals are four or five millimeters long and the limb-forming cells, though not apparent from the outside, are situated in a flat disc of tissue about 0.9 mm. in diameter, which is centered under the fourth myotome. By using a low power microscope, this rudiment can be excised with finely sharpened scissors and grafted with considerable ease. From the surgeon's point of view, the material is well nigh perfect. Nerves and muscles have not developed, so there is no sensitivity and no activity. Anesthetics are therefore unnecessary. The heart has not begun to beat, consequently there is no circulation of the blood and no hemorrhage from wounds inflicted. Furthermore, aseptic precautions are superfluous as wounds never become infected. For the first two weeks or so after operation, the embryos thrive upon their yolk and do not even have to be fed. In addition, the process of tissue repair is extremely rapid. A graft the size of the limb-bud may adhere in as few as five minutes and become completely healed in an hour.

From the results of an extensive study involving the removal or the transplantation of part of the embryonic limb-forming cells, Harrison[8] came to a number of interesting conclusions. He decided that the rudiment was an equipotential system because any part of it seemed to be capable of producing any part of the definitive limb. Its totipotentiality was indicated by the

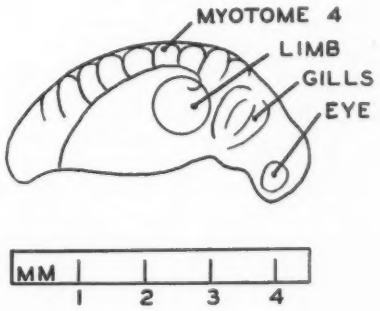

FIG. 1

Diagram of amblystoma embryo in the tail-bud stage, showing position of the limb area. A millimeter scale is shown for size comparisons.

ease with which any part produced the whole. The fact that a rudiment developed into a limb when grafted to the head or to the flank, showed it to be independent of its surroundings, at least so far as its morphology was concerned, and hence self-differentiating. Implants of disarranged mesodermal cells from the limb region into skin pockets produced normal limbs and indicated that the arrangement of the individual cells with respect to each other, played little part in determining the character of the structure produced. These findings do not apply to limbs of all animal forms, even within the same class, and it is possible that those cells responsible for regeneration of the limb may possess potencies which are quite different from those of the cells which produce the limb in ontogeny. Transplantation of regeneration blastemas has shown that the site which receives the graft may play an important role in determining the morphology of the part produced. Cells from a tail stump may produce a limb[9] and cells from the healed stump of an amputated limb may produce a lens[10] (quoted from Harrison[11]) under the influence of the proper environment. Probably these cells should be looked upon as toti- or at least multi-potent rather than as having undergone an actual transformation from one kind of differentiated cell to another.

From previous work upon asymmetrical biological systems it was to be expected that a limb rudiment, when inverted at operation, would either grow upside down, or, because of a shifting of materials, develop in normal posture. It was found, however, that when a right limb-rudiment was inverted in the tail-bud stage (*Fig. 2, A-B*), the result was a left limb (*Fig. 2, C*). Similarly, when a left limb-bud was grafted to the right side of the body, it produced a right limb (*Fig. 2, F*) if it had been inverted (*Fig. 2, D-H-E*), otherwise it developed into a left limb (*Fig. 2, D-O-E-G*). Conditions were the same, so far as the laterality of the limb was concerned, whether the graft was orthotopic (to normal location, *Fig. 2, O*) or heterotopic (to a region not designated by nature to support a limb, *Fig. 2, H*). This enigma of the change from a right limb to a left or vice versa was perplexing enough even without certain complicating factors which were often involved. In a large percentage of the grafts, made with certain orientations, not one but two limbs developed. One of these two members almost always began its development at an appreciable interval before the other, thus permitting a distinction between a primary and a secondary member of the double complex. Still further to complicate the picture, the secondary limb was practically always a mirror image of the first, with the result that the double complex was composed of a true pair of limbs, one right and one left. In many cases, one or the other of these two limbs produced further buds, which in each instance developed as the mirror image of the limb with which it was connected. All possible degrees of complexity and of anatomical relationship were evidenced by the components of these reduplicated appendages. Some were closely fused, others entirely separate.

The possibility of transformation of a right limb into a left, and vice versa, has already been mentioned. This only occurred when the orientation imposed upon the graft, at the time of operation, resulted in a reversal of the anteroposterior axis of the limb rudiment with respect to the corresponding axis of the body of the embryo which received the graft (*Fig. 2, B* and *O-E*). It was a necessary conclusion, from these experiments, that the anteroposterior axis of the limb rudiment in an embryo of the tail-bud stage of development is irreversibly polarized. That this is the only axis not subject to influences from the body of the embryo was shown by the results of experiments which reversed the dorsoventral or the mediolateral axis of the rudiment, but which left the anteroposterior axis in normal orientation. In the tail-bud stage of development, then, the limb rudiment is radially symmetrical, with only one axis irreversibly polarized. Other workers have shown that this is not the case in all embryos; the European

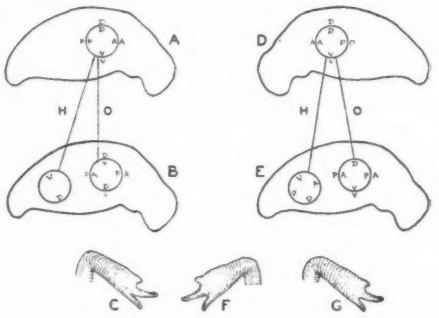

FIG. 2

Diagrams of limb grafts in various orientations with resultant limbs. A and D, donors; B and E, recipients. The circle represents the limb area, the letters within it indicate the cardinal points of the rudiment; A, anterior; D, dorsal; P, posterior; V, ventral. The letters outside the circle represent the corresponding points of the body of the embryo. H, heterotopic graft; O, orthotopic graft. Further description in text.

salamander, Triton, for instance, has two axes polarized in the tail-bud stage.

In the development of these grafted limbs it was noted that certain of those inverted on the same side of the body as that of their origin, tended to recover from the imparted position by a process of mass rotation. Some of them actually recovered their normal posture and became functional members which were indistinguishable from the normal. This phenomenon has been thoroughly studied by Nicholas,[12] who has shown that rotational recovery of posture is dependent to a considerable degree upon the normality of the girdle and its musculature. Until this process was recognized as such by Harrison, it was most confusing to the results of his investigations upon the symmetry of the limbs resulting from grafted rudiments.

From the behavior of the shoulder-girdle rudiment when transplanted, Detwiler[13] found it to be a mosaic instead of an equipotential system like the free limb. Instead of possessing the power to produce an entire girdle, portions of this rudiment merely developed as such when grafted to the flank. Furthermore, the parts left behind in normal location developed there as isolated fragments. By means of a careful series of experiments, Detwiler mapped out the location of the rudiments for the various parts of the girdle, a feat which has not yet been accomplished in the free limb rudiment because of the technical difficulties involved.

The reduplicated limbs which often result from grafts of embryonic rudiments offered a number of points for consideration. Unfortunately, it has been impossible to return any answer to the more fundamental questions involved, to-wit: why and how do they reduplicate? However, some light has been shed upon the symmetry relationships between the components in a number of the experiments carried out.[14 15] As has been stated, when a supernumerary member occurs, it is usually the mirror image of its mate. However, in a few cases of limbs grafted to normal location a combination of reduplication and rotation phenomena occurred which resulted in the production of two limbs of the same asymmetry. In these cases the primary limb derived from an inverted rudiment at least partially recovered its normal posture by rotation. During, or previous to, this process, it gave rise to a supernumerary bud. This secondary member, instead of rotating with the primary, became, in these particular cases, independent enough to differentiate in its own way and to cause little or no interference with the recovery process of its mate. According to the hypothesis advanced, the asymmetry of this secondary member was destined, from the time of its origin, to be opposite to that of the primary member, this being in accordance with the rules of minor symmetry. When, however, the primary member retained its original prospective asymmetry by virtue of its rotation and became a harmonic instead of a disharmonic member, the two components were of like asymmetry. These observations, and other subsequent ones in which reduplications were produced by inverted primary limbs,[16] have been taken as evidence that the dorsoventral axis of the limb becomes polarized with relation to the tissue immediately surrounding its base; also that the anteroposterior axis of the member has its polarity established, at the time of formation of the secondary bud, in the opposite direction to the polarization of the corresponding axis of its primary limb.

Further and earlier evidence for the truth of the statement concerning the polarization of the dorsoventral axis has been given by Nicholas.[17] This investigator transplanted a limb rudiment in inverted orientation and subsequently again inverted this rudiment plus a narrow area surrounding it. By this double operation, the limb was normally oriented with respect to the cardinal axes of the embryo as a whole, but was encircled by an inverted area. Such limbs underwent rotation to become normally oriented with respect to the surrounding area even though in so doing they rotated directly away from a harmonic relationship with the body. The process was carried out before polarization of the dorsoventral axis of the limb had taken place, so that the relative positions of dorsum and palm were not altered.

In as much as the anteroposterior axis of the limb is the only one irreversibly polarized in the tail bud stage, it becomes of some interest to find out when the other two axes of this asymmetrical system become polarized. For this purpose, and to investigate the results of grafts after two or three axes were fixed, two series of experiments were carried out on older stages.[16 18] A number of arbitrary conditions were established to rule out certain complicating factors and to reduce the possibilities of error. Briefly, to find out when the dorsoventral axis became polarized, limb rudiments of various ages were grafted to the flank in inverted orientation. To investigate the mediolateral axis,

a similar series was undertaken in which the medial and lateral surfaces of the rudiment were interchanged with respect to the body. It was found that each of these axes became fixed at a different time and both of them considerably later than the anteroposterior. Until a certain stage of development had been reached, it was impossible to secure inverted limbs, that is, limbs with the palm facing dorsally. Then, with the establishment of an unchangeable polarity in the dorsoventral axis of the rudiment, every inverted graft (*Fig. 3, B*) produced an inverted limb (*Fig. 3, C*). In the case of the third axis, the mediolateral, conditions were found to be similar though not evidenced in exactly the same manner because of the failure of reversed grafts, that is, those turned medial side laterally, to grow medially into the body. Under the experimental conditions, however, the asymmetry of the resultant limb was considered an adequate criterion of the effect and it may suffice to say that the original prospective asymmetry of these grafts was not changed after fixation of the particular axis under investigation. It was thus shown that the asymmetry of the limb is not definitely and irreversibly established until all three of its axes have been polarized. Previous to this time, it is possible to reverse the original prospective asymmetry of the limb, that is, turn a right into a left or vice versa, by proper orientation of a suitably developed graft.

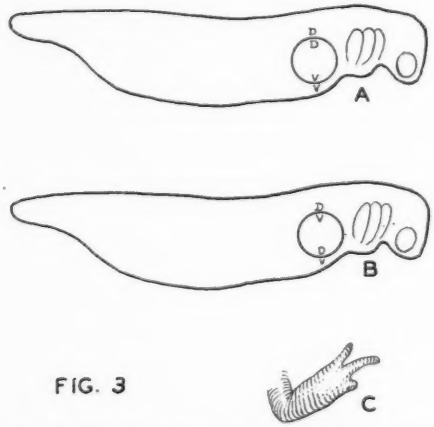

FIG. 3

Diagrams representing the operative inversion of a limb rudiment (B) and the result (C) after polarization of the dorsoventral axis has taken place. A, donor embryo with limb rudiment indicated by circle; B, recipient embryo bearing inverted graft; C, resultant inverted limb. D, V, as in Fig. 2.

Turning now for a moment to the axes of the shoulder-girdle, we find that they too appear to differentiate in a progressive fashion. As has been pointed out, the girdle rudiment does not behave like the limb rudiment when transplanted, and Detwiler[13] has concluded that it is constituted as a mosaic. Its anteroposterior axis, however, is determined early as shown by the results of the experiments carried out by Harrison.[19] The dorsoventral axis does not become irreversibly polarized until somewhat later than the corresponding axis of the free-limb. This has been demonstrated by the production of normal right girdles in connection with inverted left limbs in those cases grafted in the interval between the critical periods for polarization of the corresponding axes in the two rudiments.

The facts given above concerning the differentiation processes occurring in the limb have been brought to light by experiments involving considerable manipulation of the factors of time and the relationship of the body to the graft. They have resulted in a remarkable collection of possibilities with respect to the changeability of the potentialities and of the prospective sig-

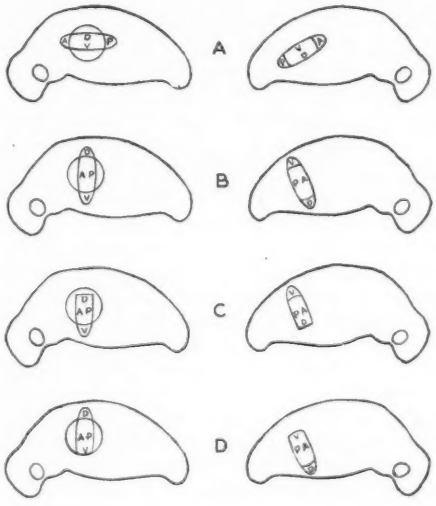

FIG. 4.

Diagrams of experiments carried out to determine location of factors responsible for polarization of the dorsoventral limb-axis. Donors are on the left, recipients on the right. Grafts all inverted. A, Inclusion of anterior and posterior tissue with part of limb rudiment. B, Inclusion of dorsal and ventral tissue. C, Inclusion of ventral tissue. D, Inclusion of dorsal tissue. Results: Normally postured limbs in A and C, inverted limbs in B and D. A, D, P, V as in Fig. 2

nificance of the embryonic rudiments in question. As an example of the practicable, though possibly not practical, wizardry, suppose we transplant a series of right fore-limb rudiments. Having suitably varied the stages used and the orientations imposed upon the grafts in the different experiments, a few days postoperative growth results in a most remarkable series of limbs. We secure four cases showing single limbs, two of which are rights, the other two lefts, one of each right side up, the other inverted. Next, we have individuals showing two limbs which have developed from the graft. These double complexes differ from each other in that one shows both components to be rights, in another they are both lefts, while in a third, one member is a right and the other a left. Further cases in this group of doubles show more members arranged as above, but in all possible combinations of inversion and of normal posture between the components. Further, we have a group in which three or four limbs developed from the graft, each complex exhibiting more or less consistent mirror-image relationships between the components. To complete the series of weird results, a dissection of certain of the preparations reveals left limbs articulating with right shoulder-girdles, the former inverted and the latter right side up.

The explanation of these conditions, which are readily obtained by experimental methods, lies in the progressive differentiation of the three axes of the limb and in the fixation of the dorsoventral axis of the shoulder-girdle. The occurrence of a time factor in the differentiation of the limb has been demonstrated by these experiments and by other observations on the limbs of different forms. The processes leading to the establishment of limb asymmetry have been shown to be manifold, and to be affected, to a certain extent and under certain conditions, by the influence of the body upon the developing limb.

It appears to be impossible to study, by our present experimental methods, the factors responsible for polarity fixation in the anteroposterior axis of the limb rudiment because the process takes place very early in development.[20] The dorsoventral axis, however, becomes fixed at a later time, not only enabling us to find out when its polarity is established; but also, by including with inverted grafts extrabrachial tissue from different neighboring sectors (*Fig. 4*), to show[21] that only the portion located dorsal to the rudiment is effective in preventing the reversal of axis polarity usually consequent to its operative inversion. Efforts to isolate the factors responsible for polarity fixation, or its reversal, have not met with signal success; nevertheless they are not without interest from the point of view of the present discussion. For example, suprabrachial or dorsal flank tissue was grafted[22] in inverted or in normal orientation, dorsal or ventral to limb rudiments (*Fig. 5*). When the latter were inverted at operation and the dorsal tissue inserted ventral to them (*Fig. 5, B*), a considerable proportion evidenced the effect of this relationship by the production of inverted limbs. Or perhaps more accurately put, the production of inverted limbs indicated the absence or the non-effectiveness of surrounding factors which, had the dorsal tissue not been present, would have caused a reversal of the original prospective polarity of the axis as evidenced by the normal posture of the resultant limbs. The dorsal tissue thus seemed to serve as a block to factors or forces resident in the area surrounding the graft-site. That its own orientation is not important is shown by the inverted posture of limbs properly related to normally postured as well as to inverted dorsal tissue. That it is not actually a determiner or organizer of the dorsoventral axis is shown by its failure to function when placed at the ventral end of the operatively inverted axis, that is, between it and the dorsal midline of the embryo (*Fig. 5, A*), or to reverse a non-inverted axis

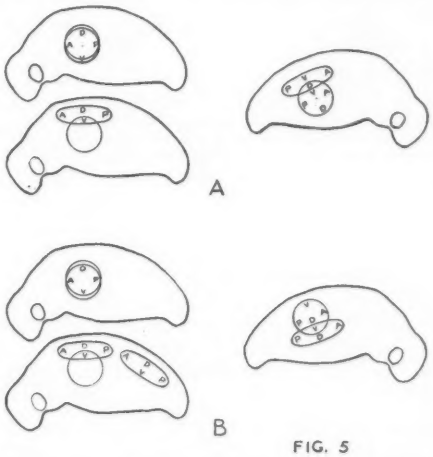

FIG. 5

Diagrams of double operation involving a limb graft to opposite flank followed by transplantation of a dorsal (oval shaped) patch either dorsal (A) or ventral (B) to the grafted limb. Donors on left, recipients on right. A, D, P, V, as in Fig. 2.

from either end. Still further evidence in support of the idea that the dorsal tissue serves as a block, rather than as an active agent, is given by the results of limb grafts to the lateral surface of the myotomes. In this location the dorsoventral limb axes underwent no reversal when inverted at operation, the definitive limbs being upside down (*Fig. 6, B*), quite the opposite from the results of many operations exactly similar except for placement of the graft a fraction of a millimeter further ventral on the body wall (*Fig. 6, A*). The flank position, in itself, might be considered effective had not inversion there also been demonstrated after subjacent myotome tissue had been provided by means of a second operation (*Fig. 7*).

Experiments designed to investigate the time factor in this limb-axis differentiation have not proven entirely satisfactory. Whatever the influences may be which fix the axis polarity, they are singularly ineffective in reversing it when once it is established. This has been shown[23] by the results of grafts made from older to much younger embryos. Likewise, attempts[24] to delay the process by temporary subjection of grafts to influences from a younger embryo body have been completely negative. The results showed very clearly that there had been no change in the rudiment which could be ascribed in any way to possible factors in the younger body. The nature of the experiment permitted no conclusion as to whether the axis became polarized as a result of a carry-over of possible pretransplantation influences brought to bear upon it by the donor, by a premature effect exerted by the younger tissues of the recipient; or as to whether temporal self-differentiation is a function of the rudiment itself.

Singularly inconstant have been the results[25] of several series devised to test the possibility that exposure of a younger limb rudiment to an older environment might result in a precocious polarization of this axis. In spite of the wide variation of the results, which indicated that the surroundings had some effect upon the rudiment, there was no conclusive evidence of change in the speed of differentiation.

Nevertheless it has been shown that age differences between donor and recipient may alter

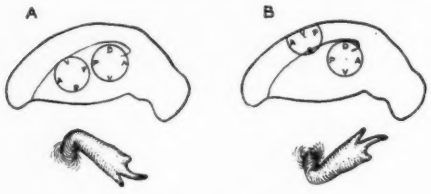

FIG. 6

Diagrams of limb grafts to flank (A) and lateral to myotomes (B) and showing the posture of the resultant limb in each case. See text for further explanation. A, D, P, V, as in Fig. 2.

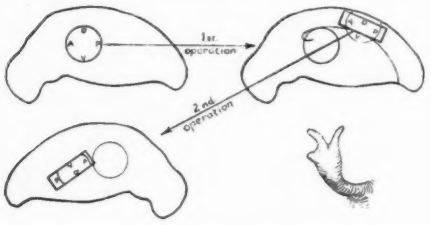

FIG. 7

Diagrams of a double operation by which limb-forming cells were grafted lateral to myotomes at first operation, then removed with myotome tissue and transplanted in inverted orientation on the opposite flank at second operation. The inverted limb resulting is also shown. A, D, P, V, as in Fig. 2.

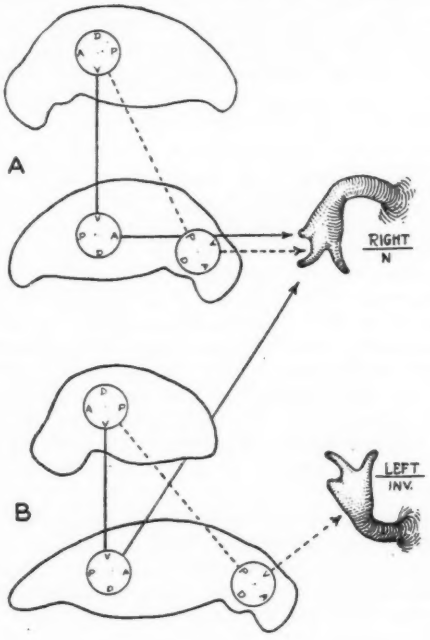

FIG. 8

Diagrams showing results of operative inversion of the dorsoventral limb previous to its polarization. when donor and recipient are the same age (A) and when they are of different ages (B). The younger graft to the older head is the only combination which results in inversion of the definitive limb. A, D, P, V, as in Fig. 2.

the results under certain circumstances. As pointed out above, operative disorientation of the dorsoventral axis of limb rudiments transplanted in the tail-bud stage of development has not produced disorientation of the corresponding dorsopalmar axis of the definitive limb. However, when the donors were considerably younger than the recipients and the grafts were made to the head, inverted rudiments produced inverted limbs[25] (*Fig. 8, B*). This finding would appear to indicate that whatever factors, capable of changing the prospective polarity of the axis, may be present in the younger head (*Fig. 8, A*), and in the lateral plate mesoderm of the trunk at all ages tested, they are either absent from or ineffective in the tissues of the older head. It would be interesting to see whether appropriate operative association of limb rudiments with unsegmented axial mesoderm might not produce results bearing to those derived upon myotome sites the same relation which has been shown to exist when younger versus older head-sites were used.

It has been somewhat of a temptation to speculate, from the results of these experiments, upon the matters of physiological gradients and progressive losses of potency paralleling differentiation. Such a flight is hardly justified by these results alone and the scope of this paper would be broadened too greatly by adequate discussion of the vast number of studies by which many other investigators are contributing to the general problem. A large amount of work remains to be done, perhaps much of it with different technics carried out upon different material. Our chief hope for the brief outline given here is that it may have some provocative value toward future thoughts along the line of cellular differentiation and of possible inter-relationships between embryonic cells. As Harrison[11] has stated in a recent review of the relationship of embryology to other fields:

"Substances that react with the living protoplasm * * * may arise from many sources. They may diffuse into the oocyte from maternal tissues; they may arise from the genes in the nucleus; they may come from organizers, i. e., from other cells in close contact with the cells affected; they may be transported in later stages through the circulating body fluids (hormones), and finally they may come from the external medium. There is no reason to think that there is any fundamental difference in the action, on the living protoplasm, of substances derived from these various sources. Much depends, however, upon the time at which the protoplasm is most sensitive to their action." (p. 373)

Our observations and experiments themselves, of course, have no direct bearing upon the problems of the pathologist. The principles involved, however, may perhaps be looked upon as fundamental in cellular physiology and herein lies their value for the pathologist. Disrupted cell functions must be charged with the responsibility for the very existence of pathology. Only so far as we can control the responsible causes, in terms of cell functions, may we have the hope of finally understanding what anatomy and pathology really are.

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THE PRESENT STATUS OF GASTROSCOPY*

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Gastroscopy is one of the newer diagnostic methods. Presented some years ago, it carried us a long step forward in gastric research by permitting direct inspection of the gastric cavity; and now, because of the development of the flexible gastroscope, it offers still greater possibilities. However, the widespread popularity attained by this adjunct to our diagnostic armamentarium carries certain disadvantages in the way of exaggerated claims as to its adaptability and value. I therefore think it wise to review at this time the possibilities of gastroscopy as well as the handicaps under which gastroscopists must labor.

It may be said, without undue pessimism, that

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the medical profession as a whole is all too ready to accept without sufficient study practically every attractively presented type of diagnostic method and treatment. Surely anything which promises to be of value deserves calm appraisal of its virtues and sane discussion of its limitations.

The continuing tragedies in relation to sulphanilamide are a devastating commentary upon the downright gullibility and utter lack of judgment in many otherwise conscientious members of the profession; one questions the adequacy of medical training which permits acceptance of unproven claims on any product or any method.

I defer to no one in my belief and confidence in gastroscopy as an excellent method of diagnosis; however, it is certainly not yet dependable in all cases; it has not even approximated a state of perfection, and I feel that we should consider its present drawbacks from three angles.

(1) *Technic.*—While this is not too difficult to master, it is not quite so simple as many gastroscopists would have us believe; undoubtedly there is still risk of perforation unless the instrument is handled with meticulous care; and force is above all things to be avoided. Actual observation of the procedure of introduction will convince most individuals of the accuracy of these statements. Only after thorough training, should the beginner be allowed to essay introduction of the gastroscope, and even then he should be under the eye of an expert.

(2) *State of Development of the Instrument.*—As I said before, the instrument has by no means reached perfection, and as yet one cannot obtain a wholly satisfactory view of the entire stomach; in fact, in many instances the existence of anatomical deformities and anomalies allows inspection of only a very circumscribed area.

(3) *Interpretation of What Appears Through the Lens.*—I wish to emphasize very strongly that we are still far from solving this problem of interpretation and the accurate differentiation of various gastric lesions which it involves. It is true that great strides have been made, but I am not ready to accept the extremely optimistic reports of some authorities who believe that mere observation of the mucous membrane enables them to make an immediate accurate diagnosis.

An eminent gastroscopist recently remarked to me that he had watched the work of a skilled colleague who labeled fifteen successive cases "gastritis," though the observer himself would have called all fifteen stomachs normal, merely noting the changes in color and the moderate physical differences which to him did not represent disease.

The whole subject seems to me only in the experimental stage, and I believe that gastroscopy as a valuable diagnostic method will be irreparably harmed by hasty and unscientific approach; its potential worth is so great that it deserves a more judicial attitude on the part of its protagonists.

Membranes in different organs of the same individual will vary in appearance, just as faces in a group of people will differ without the slightest evidence of disease. So it is with the mucous membrane of the gastric cavity; varying hues and characteristics need not necessarily be labeled abnormal. It is my firm conviction that time must be allowed for exhaustive research on hundreds, indeed thousands, of cases with comparative studies of the findings by skilled men; only when these results are available to students of gastroscopy can we feel that the instrument has fulfilled its promise as a diagnostic aid.

In gastroscopy, the lesions which occupy our attention are the gastritides, with or without superficial and deep ulcerations, peptic ulcer, lesions due to allergic reactions, carcinoma, benign tumors.

In regard to the gastritides, I consider Schindler's[18] classification the simplest, that is, superficial, hypertrophic, atrophic. Further, in reference to gastritis, Gaither and Borland,[1] in a previous communication, inquired as to whether it is not more important to consider severity, location and extent, rather than actual type. In view of the many questions that arise, it seems unwise to consider our present observations final; certainly there is much to be done before correct interpretation is assured.

After classification, the next point of great importance is that of indications and contraindications for gastroscopy. Most gastroscopists appear to feel that every case presenting digestive symptoms should be gastroscoped. I prefer to select cases for gastroscopy only after mature deliberation as to whether the procedure is justified.

Gutzeit[7] advocates gastroscopy wherever it is possible to introduce a soft rubber tube. Henning[8] declares that modern gastric examination is not complete without gastroscopy, if the x-ray examinations reveal either ulcer or carcinoma:

also if x-ray shows a pathologic mucosal relief; he further states that he does not so often find ulcer in the gastroscopic mirror as the x-ray would lead us to suspect. In his last thousand gastroscopies he had no mishaps.

The patients who certainly merit gastroscopic investigation are postoperative cases with recurrent digestive symptoms, and those suspicious of a serious lesion, or presenting persistent symptoms in which x-ray examinations are uncertain or completely negative.

Jackson[9] recommends gastroscopy in order to remove foreign bodies from the stomach; he also considers it of great diagnostic value in supradiaphragmatic stomachs; of the latter, the greater number have been sent to him with a diagnosis of carcinoma of the esophagus. He says, "Every patient with gastric symptoms should have a gastroscopic examination for diagnosis unless there are overwhelming contraindications."

Among the indications for gastroscopy, the most important is that which signals the beginning of neoplastic infiltration.

Practically the only contraindications universally acknowledged by endoscopists are cardiovascular disease (aneurysm, angina, and any other pathologic states in this domain) and mechanical obstruction of the esophagus or cardia. Some authorities list in this group a large diverticulum. Many believe that recent hemorrhage is by no means a contraindication, but rather a definite indication of the necessity of gastroscopy for location of the lesion and determination as to its character. I am unable to concur in this opinion.

Not only are we as yet unable to differentiate by direct gastroscopic inspection a benign from a malignant ulcer, nor to assure ourselves that the process represents a slowly advancing, small, ulcerating carcinoma, but we are also powerless to cope with the problem of differentiating the types of atrophic gastritis which may accompany pernicious or secondary anemia, or an atrophic gastritis which is found at times with a normal blood picture.

Certain it is that we have not attained a definite unerring criterion for each disease entity, and cannot lay claim to finality in our observations; we must, therefore, be patient and thorough in our efforts to establish a satisfactory classification, anticipating this as an ultimate goal. Unsolved problems such as these should be incentives rather than deterrents.

I am convinced that in most cases the intragastric picture observed represents the different stages of one and the same process, though it is conceivable that independent changes can and do occur in various areas, such as superficial or rather deep circumscribed ulcerations in the midst of an area of gastritis or carcinomatous degeneration at the site of a benign ulcer.

Where a true gastritis has been established, gastroscopy will help us to find and follow transitory changes in the mucous membranes such as inflammation, ulceration, hypertrophy, atrophy, hemorrhage, localized injection, edema, and allergic reactions brought about by food, drink, or bacterial activity. Marked changes in the color of the mucous membrane are an outstanding characteristic.

Schindler[20] states that he has examined gastroscopically more than twenty-five hundred patients, all of whom had abdominal complaints. Twenty-three per cent of this group had normal stomachs gastroscopically, as judged by the appearance of stomachs in healthy persons without evidence of any disease. About 50 per cent presented mucosal changes similar to those of chronic inflammation of other mucous membranes.

Gastroscopy has shown without shadow of doubt that the basis of many chronic digestive symptoms hitherto labeled nervous dyspepsia and digestive neuroses, is none other than an ingrained and advanced gastritis.[6 8 11 12 13] The symptoms which this disease entity provokes may mimic any syndrome resulting from various intra-abdominal lesions. I believe that gastritis cannot be diagnosed or confirmed with certainty by x-ray alone, and that gastroscopy is the only sure means of identifying this important and widespread disease entity, and of making an accurate diagnosis.[10 21 22]

It is interesting and enlightening to consider Gutzeit's description of the findings which to him are indicative of gastritis.

"Its characteristics are uneven spots of altered blood distribution, edematous areas with abnormally smooth or dry, fissured, roughened and thickened surfaces, abnormal reddening indicating hyperemia, or hemorrhage; epithelial defects, erosions, ulcerations. Then come hypertrophic excrescences, beside the atrophies, mucosal oozing, thickened leukocytic secretions and general alteration of caliber of the folds, as well as their course and their elasticity; these occur because of the narrowed arrangement of the folds pressing on the swelling."

This author groups the gastritides as: (1) tumor-catarrh, (2) hypertrophic, (3) atrophic. My experience is that in many cases it is quite

difficult to draw a sharp line of demarcation between the various types.

Gutzeit claims that chronic gastritis is the most frequent disease of the stomach, twelve times more frequent than gastric ulcer, and three times the incidence of duodenal ulcer; he also affirms that gastritis is definitely a localized disease, and that erosions, ulcerations and true niche ulcers occur only in simultaneously gastritically changed stomachs. He further says that behind every chronic achylia stands a chronic gastritis. It is his experience that the worst forms of gastritis occur after stomach operations, and that anastomosal openings are frequently surrounded and sometimes narrowed by indurated protuberances of excessively swollen mucosa.

In regard to the question as to whether gastritis is pre- or postoperatively developed, it is his opinion that in every operation for an ulcer of long duration, gastritis had certainly been present before operation; and if operation takes place in a severely inflamed area, this inflammation is exacerbated by the incision itself, and leads to a further outbreak in the anastomosed jejunum. Chevallier's researches led him to the same conclusion.

Gastroscopy should prove valuable in completing a diagnosis, and also in watching the results of therapy in cases of peptic ulcer. When no contraindications exist, repeated gastroscopies will aid us to exclude or to prove the presence of an accompanying gastritis, localized, general, mild or severe, with or without superficial ulcerations; and since gastritis often, if not always, accompanies peptic ulcer, we should not be surprised or disappointed if after surgical interference the postoperative course is not so smooth, brief nor successful as we had anticipated. In these cases, gastroscopy gives a picture of a well-established gastritis of varying types, often showing, in addition to the inflammatory tissue, superficial or fairly deep erosions.

Such gastroscopic information as to the presence of gastritis will prove the necessity of prolonged postoperative care as to hygiene, diet and medication. On the other hand, those who advocate bold resection would feel justified in radical surgery, being assured that if this diseased portion of the stomach were not removed, untoward postoperative results would follow. My own views on the subject are that successful results, both postoperative and non-operative, may be hampered or even prevented by a residual and markedly advanced gastritis.

Some authorities claim for gastroscopy a double preliminary value; it not only locates very precisely the seat of the inflammatory lesion associated with ulcer, thus facilitating the choice of operation, but it also allows a preview of the extent of eventual resection by estimating exactly the limits of the gastritic process. These men consider that gastroscopy is thus clearly superior to all information which blind palpation can furnish in the course of operation. We see, therefore, that gastroscopy, through direct view of the mucosa and its coloration, really allows us to outline with precision the inflammatory reactions associated with gastric ulcer, and gives the surgeon not only a choice of operation, but also an opportunity for postoperative prognosis.

Many authors have an unshakable belief that a peptic ulcer is likely to yield to treatment much more readily than gastritis, particularly if the latter has reached an advanced stage. Various authors have noted marked vascular friability and a decided tendency to bleed in quite a number of cases of gastritis. In this respect, it is interesting to note that Schindler has called attention to gastric purpura and to the fact that it may or may not coincide with cutaneous symptoms. Chevallier[2] and Moutier[16] have reported a gastric purpura in an acute inflammatory purpura with cutaneous eruption, and abdominal pains, the mucosal eruption resembling cutaneous eruptions; these were observed in all portions of the stomach. The same authors report a single case of gastric hematoma, a lesion which is undoubtedly rare.

These gastroscopic observations demonstrate the value of the instrument in enabling research workers to bring to the light of day varied and interesting intragastric disease entities.

I believe that when gastroscopy has been more deeply studied and is more discriminatingly practised by skilled operators, there will be discovered a large number of ulcers which had been absolutely unsuspected either clinically or radiologically; among these there will doubtless be many potential bleeders, the hemorrhage being either frank or occult in type.

There is widespread and anxious hope that further development of this method, as well as continued clinical investigation, will lead to an earlier diagnosis of cancer of the stomach; it is fully realized that at present, infiltration of the gastric wall often becomes serious before x-ray and laboratory examinations can furnish the first suspicious indications.

Chevallier[5] and Paviot[17] present an endoscopic finding which they think is clearly indicative of early carcinoma, justifying exploratory laparotomy. They state that there is a definite leuko-atropho-amyxic state of the antrum with pyloric deformity which is permanent; however, it is important not to confound this picture with the diffuse localized atrophy which is sometimes observed in pernicious anemia. They assert that this endoscopic syndrome should be systematically sought in all gastropathic cases in adults who do not yield quickly to treatment.

It is certain that this direct method of search gives us more hope of discovering early structural evidence of carcinomatous growth than any means so far devised; indeed, I think it not too much to expect that eventually we may in many cases be able to identify pre-cancerous conditions with a hope of effective prophylaxis. Furthermore, it may be our good fortune to find and properly interpret the non-cancerous lesions which at times form the basis of the cancer. The attainment of this desired goal will of course require innumerable gastroscopic studies, but, as we have learned in other fields of research, seemingly impossible tasks are always accomplished in due time.

Eminent authorities have asserted that chronic gastritis, especially when accompanied by hypochlorhydria or achlorhydria, represents a field favorable for the development of carcinoma. Such a theory has not been definitely proven, however.

As yet, no authority has claimed familiarity with the special endoscopic indications which would permit us to foresee the cancerization of a peptic ulcer, nor to predict whether the ulcer will be active, chronic, or calloused. It seems pertinent to mention here the undoubted fact that a large number of so-called cancerized ulcers are in truth slowly developing cancers of an ulcerative type, and that when radiologic signs are clear, the tumor is already very large, and too often inoperable. We can readily realize from these facts that it is at this moment endoscopically impossible to differentiate between malignant transformation of an ordinary ulcer and a slowly-growing ulcerating cancer. The present endeavors of the gastroscopist must therefore be focused upon an early diagnosis of confirmed cancer; when this step is accomplished, the rest must follow.[23]

It has been suggested, rightly, I think, that when the intragastric picture presented is too indefinite to justify operation, successive gastroscopies should be the method of choice for early detection of the first signs of degeneration; and in view of the very slow development of many cancers, this method of observation may lead us to life-saving therapy. We must exert every endeavor to become expert in the interpretation of doubtful pictures; it is because of our inability to interpret properly what we clearly see, that endoscopic diagnosis in early stages of gastric cancer has been attained in so few cases. The fault lies, therefore, not with the method, but with the man.

Paviot and Chevallier[17] present facts in favor of the allergic nature of a certain number of gastropathic pseudo-lesions. They believe that radiologic examinations in the course of the paroxysmal occurrences of these gastropathies reveal pictures that are somtimes typical, always variable and transitory, simulating the most severe organic lesions. Furthermore, gastroscopic examinations also show during the course of gastralgic crises (either spontaneous or provoked by ingestion of specific alimentary antigens), lesions of the gastric mucosa that are edematous, hemorrhagic, or erosive; these are variable and transient. These authors describe a very interesting finding in a case of allergic outbreak. The gastroscopic investigation showed a typical transitory antropyloric edema which completely masked the pylorus; this edema suddenly disappeared at the beginning of the period of relief. Another interesting case in this series presented an ulcer syndrome; operation failed to reveal an ulcer. Gastroscopy during a crisis showed several quite superficial erosions, oval in shape, yellowish-green at the base, located on the lesser curvature near the gastric angle. Erosions were also observed at the upper part of the antral sphincter; in the same zones the gastric mucosa presented a more or less succulent appearance. Specific desensitization caused the lesions and symptoms to disappear entirely.

These authors present another group of extremely interesting findings which I shall mention only briefly: (1) digestive hemorrhages without signs of sensitization, and without gastroduodenal lesions (x-ray and gastroscope); (2) digestive hemorrhages without duodenal lesions (x-ray and gastroscope) with signs of sensitization; and (3) digestive hemorrhages with obscure and transitory lesions under the gastroscope, and allergic signs.

Finally, Chevallier and Paviot describe a type

of allergic pseudo-cancerous syndrome with varying x-ray results, the gastroscopic study revealing unstable and transitory edema very definitely limited to the antropyloric regions, and exactly superposed upon the radiologic images. We thus see that the gastroscope opens up another very important and fertile field of investigation.

Chevallier's conclusions are most instructive as regards endoscopic aspects of the gastric mucosa in 40 subjects presenting a syndrome of ulcerative type; in 19 cases, of which six presented x-ray signs of ulcer, the mucosa was absolutely normal. In eight cases, there were definite gastritic lesions. In five cases, repeated gastroscopies showed an edema "a l'eclipse" of the antropyloric region which seemed to be one of the anatomo-pathologic elements of the substratum of allergic gastropathy. In seven cases, there was typical ulcer of the lesser curvature and prepyloric region, with absence of x-ray signs; in three cases, superficial ulcers were noted. The gastroscope permitted the workers to realize the extent and intensity of the associated gastritis. In one case, prepyloric ulcerocarcinoma was verified operatively.

Gastroscopy appears to be the method of choice in the depiction of beginning gastric cancer. Moutier has done much investigation of the gastric mucous membrane in anemias, and states that gastric atrophy is the rule in hyperchromic anemias, inconstant in hypochromic anemias, and most often absent in normochromic anemias of the pure aplastic type. He makes this reservation, however: "Atrophy is not truly constant except in the hyperchromic megalocytic and megaloblastic anemias of the pernicious type."

It is Chevallier's opinion that any operative decision in an anemia presenting canceriform gastric images on the screen must be preceded in the future by gastroscopic examination; and he concludes that gastroscopy is truly the method of choice, not only to confirm (by revelation of gastric atrophy, mostly zonal), a rather uncertain diagnosis of pernicious anemia, but also to disclose in good time an associated cancer, primary or secondary; or, one may discover the ephemeral evolution of those anemia-edemas which may assure in pernicious anemia the radiologic appearance of a proliferating cancer of the stomach.

It has been shown definitely that diffuse superficial changes such as gastritis, atrophies, hemorrhage and varices are not accessible to x-ray, and can be perceived with certainty only under the gastroscope. It is true that one gastroscopic examination is often insufficient to give a conclusive idea as to the condition, for there is in the gastroscopic picture no assurance as to whether what one sees is a permanent end-result or an active process. The answer to this difficulty is successive examinations plus all other possible clinical investigations. However, there is no gainsaying the fact that gastroscopy can at times be of conclusive early diagnostic value when significant clinical findings have not been confirmed by x-ray.

Gutzeit gives an excellent description of a malignant lesion as revealed by the gastroscope:

"Heavy, rough swellings on an inflammatory base, with a far-spreading change in fold-relief, are the characteristics of the endoscopic carcinoma diagnosis. At times we find hemorrhage in the ulcerated portions, necrotic, whitish glistening coatings both superficial and deep, irregular filling defects with jagged raised edges."

It is also Gutzeit's opinion that benign tumors may be differentiated from cancer by their much more irregular surface and infiltration.

In conclusion, I desire to emphasize the fact that the object of this presentation is to discuss in a comprehensive manner a most important addition to our diagnostic armamentarium, directing attention to its limitations as well as to its outstanding advantages, with emphasis on the former in order that we may not allow our enthusiasm for its value to outweigh our good judgment. Much remains to be done before its possibilities for good are thoroughly explored and developed; but because of my personal observation of its present application to the diagnosis of diseased conditions in the gastric domain, I willingly venture the prediction that with proper study, and in proper hands, this most valuable diagnostic procedure will eventually prove of permanent benefit to mankind.

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DISCUSSION (*Abstract*)

Dr. James L. Borland, Jacksonville, Fla.—Dr. Gaither has been eminently fair in his summary of the value and use of gastroscopy. One year ago I read a paper on gastroscopy before this Association. Since that time I have modified my ideas considerably, particularly concerning gastritis. I am very much less certain as to what constitutes clinical disease and what does not. I am just as certain as I was then that, in a large proportion of patients who have gastric complaints, the gastric mucosa shows evidence of inflammation and chronic irritation. I am sure that in the severer cases this inflammation causes symptoms. Whether or not one may call any of the lesser changes in the stomach clinical disease or not remains uncertain. As in the pharynx and many other organs it may be that the degree is the all-important feature. I do not believe, however, that it is fair to say that because mild degrees of inflammation elsewhere do not cause symptoms that this is true also of the stomach. The stomach is a specialized organ and the changes may bring about physiological and clinical effects more easily.

It has been my experience so far and I believe the experience of most of the gastroscopists that when one sees these inflammatory lesions once, one always sees them in the stomach, no matter how many times it is examined. The stomachs that seemed normal at the first examination appear healthy at subsequent inspection. This extraordinary constancy of findings gives some weight to the idea that we are dealing with disease entity and that its recognition, no matter how slight, is important.

Another difficulty in interpreting color variations and lesions is our lack of accurate information concerning physiological variations. The actively secreting stomach shows the most marked changes. The mucosa is fiery red with occasional red blotches, with adherent and stringy mucus on the sides, even at times hemorrhagic areas. In short, the secreting stomach appears inflamed. We need to know how much food is necessary to produce activity. Is there any characteristic momentum or habit of secretion so that the gastric mucosa in some patients might still be secreting the day following cessation of food intake?

Dr. V. P. Sydenstricker, Augusta, Ga.—Until recently, gastroscopy has been so difficult that it has been limited to the practise of our most skilled endoscopists. This group of specialists has emphasized the importance of direct inspection of the stomach and it is to them that we still must look for refinement of instruments and technic and for the establishment of adequate criteria of diagnosis. It would be most unfortunate if the present wave of enthusiasm inspired by the invention of the flexible gastroscope resulted in its indiscriminate use by untrained observers, however earnest.

The value of any endoscopic examination depends on the experience of the observer. The wide range of normal aspects of the hollow viscera makes casual or occasional endoscopy almost valueless. Skillful gastroscopy, however, adds an invaluable aid to diagnosis in a most difficult field. All internists know the limitations of the information obtained by ordinary methods of examination of the stomach. Test meals of various sorts tell us something of the secretory activity of the mucosa and suggest the presence or absence of ulcerative or inflammatory processes. Skillful x-ray examination reveals the size, position and motor function of the organ and the presence of gross lesions. Direct inspection alone can give information regarding the state of the gastric mucosa, the presence of superficial ulcers, of edema and of atrophic and hypertrophic changes.

It would seem proper to urge the practice of gastroscopy by specialists in your field. It seems destined to become as necessary a part of adequate gastric examination as cystoscopy is in the practice of urology. Gastro-enterologists have almost unlimited opportunity to observe all types of functional and organic disturbances of the stomach. It is equally important to discourage casual gastroscopy by so-called diagnosticians.

Gastroscopy has restored the diagnosis of gastritis to a place long made vacant by the pessimism resulting from inadequate diagnostic methods. It will be most interesting and helpful to watch the development of the final diagnostic criteria in this condition. What proportion of patients with so-called nervous indigestion and gastric neuroses have actual gastric disease remains to be seen. It is likely to be considerable. With visual guidance we may be able to refine functional and radiological diagnosis immensely.

The state of the gastric mucosa directly observed in Addisonian anemia, pellagra and sprue offers a wide field for investigation. Gastric allergy has already been identified and a number of gastroscopic appearances described. Much remains to be learned. Gastric ulcer is certainly more often recognized by inspection of the stomach cavity than by any other means of diagnosis. The identification of precancerous lesions and early cancer awaits further study, as does the problem of gastric syphilis.

The internist, the surgeon and the general practitioner seem destined to rely on gastroscopy for accurate diagnosis as they now depend on cystoscopy and bronchoscopy. The gastro-enterologists are the group who will be called upon to make the examinations and diagnoses. It should not take many years for accurate diagnostic criteria to be established in many of the more baffling gastric disorders and rational treatment is certain to follow adequate diagnosis.

FOOD ALLERGY AS A CAUSE OF VASOMOTOR RHINITIS*

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In previous communications,[1] it was stated that the ingestion of food induced nasal symptoms in certain individuals. Additional patients have been studied in the manner previously described, and now it is possible to report the clinical observations upon 181 patients in whom the deliberate ingestion of food induced nasal obstructions, coryza, and sneezing, one or all, of varying intensity. This accession has produced changes in the statistical data of the previous communications and has given the opportunity to determine the influence of clinical food sensitivity upon the therapeutic result.

Cutaneous tests were done by the percutaneous and intracutaneous methods, routinely with 26 inhalants, 51 foods, 43 pollens, and such other substances as were indicated by the clinical history, and in recent years, the available molds. They were recorded as positive when differing from the control tests because therapeutic experience has shown that clinical sensitivity is indicated by weak or small, as well as by strong or large skin reactions, so that for the purpose of diagnosis there is no practical need to record their size. On this basis, 170 cases gave positive skin reactions and 10 (5 per cent) gave no skin reactions (2 cases of angio-edema, 6 cases of perennial vasomotor rhinitis, and 2 cases of perennial vasomotor rhinitis and asthma), and in one case all substances reacted with a papule and an erythematous halo so that there could be no certainty about the interpretation of the tests. Skin sensitivity to more than one genus was the rule; there being 23 instances (13 per cent) of cutaneous reactions only to foods (18 cases of perennial vasomotor rhinitis and 5 with a presenting symptom other than nasal), and one instance of skin sensitivity only to pollen.

As the result of repeated deliberate feedings of the food suspected, either from the positive

Table 1

FOODS INDUCING NASAL ALLERGY BY DELIBERATE INGESTION IN 181 CASES

	Hay Fever	Hay Fever and Asthma	Perennial Vasomotor Rhinitis	Perennial Vasomotor Rhinitis and Asthma	Other Allergic Manifestations with Nasal Symptoms	Total
Wheat	7	6	25	13	10	61
Chocolate	3	4	25	4	8	44
Egg	6	4	18	2	5	35
Milk	3	1	10	5	7	26
Beans*	6	4	8	3	..	21
Peas	2	2	8	4	2	18
Potato	1	5	4	6	1	17
Tomato	1	2	11	1	1	16
Corn	3	..	6	5	2	16
Beef	1	2	9	1	2	15
Onion	1	3	7	2	2	15
Pork	..	1	10	1	1	13
Fish†	3	2	3	4	1	13
Nuts‡	..	2	7	1	..	10
Cantaloupe	2	4	1	2	..	9
Peanut	2	1	1	2	2	8
Black pepper	1	2	3	1	1	8
Chicken	1	2	3	..	..	6
Asparagus	..	1	2	2	1	6
Orange	..	..	4	..	1	5
Apple	1	..	3	..	..	4
Grape	..	1	2	..	1	4
Cabbage	2	..	2	..	..	4
Rice	1	..	2	1	..	4
Liquor	..	1	2	1	..	4
Peach	..	1	2	..	..	3
Spinach	1	1	..	1	..	3
Almonds	2	..	1	..	..	3
Watermelon	..	1	2	..	..	3
Grapefruit	..	1	1	..	1	3
Pineapple	..	..	3	..	..	3
Ginger	..	1	1	..	1	3
Lettuce	..	..	2	..	1	3
Mint	..	..	1	1	1	3
Oat	..	..	1	2	..	3
Lamb	1	..	1	..	1	3
Spices§	..	..	2	1	..	3
Cinnamon	..	1	1	1	..	3
Carrot	2	..	1	..	..	3
Strawberry	1	..	..	1	..	2
Sweet potato	..	..	..	1	1	2
Cucumber	1	1	..	..	..	2
Cherry	..	..	2	..	..	2
Cheese	1	..	1	..	..	2
Cauliflower	..	1	1	..	..	2
Cocoanut	..	1	1	..	..	2
Green pepper	..	..	2	..	..	2

Once each of tea, raspberry, blackberry, cloves, garlic, rye, veal, chicory, mustard, celery, plum, lemon, parsley in perennial vasomotor rhinitis.

Once each of radish and rhubarb in perennial vasomotor rhinitis and asthma.

Pear once in hay fever and asthma.

*Includes string beans and lima beans.

†Includes all fish without regards to species.

‡Includes all nuts except almond.

§Includes a mixture of spices commonly used for seasoning and flavoring.

*Read in Allergy Clinic and Round Table, meeting conjointly with Southern Medical Association, Thirty-First Annual Meeting, New Orleans, Louisiana, November 30--December 1-2-3, 1937.

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skin test or the dietetic diary, when the patient was free of symptoms, 36 cases (19 per cent) were found to be sensitive to one food and 145 cases to more than one food, the greater number of these to either two, three or four foods. The group as a whole was clinically sensitive to 278 foods, which gave 170 positive skin tests according to the described criterion. It is not possible to present figuratively the diagnostic efficiency of the skin test in these clinically sensitive cases, but in all but a few instances it indicated at least one of the offending foods. Further, each patient brought up for consideration a distinctly individual problem. It was impracticable to feed all the cutaneously reacting foods in every case. The rule was to observe the effect of the foods most important in an adequate and balanced diet, and such other foods as the patient desired to eat.

Wheat was the most frequent causative agent by fed test for the whole group; followed by chocolate, egg, milk, beans, and other foods in decreasing frequency, maintaining the same ratio in the clinical subdivisions except in the instances of perennial vasomotor rhinitis, in which pork and tomato were proportionately more frequent causative agents.

There are 32 cases of hay fever. All gave positive cutaneous reactions to pollen, with 17 of them reacting also to food and 14 others to food and inhalants other than pollen. One gave no skin reactions to foods, but had a better clinical result when milk, eggs, and wheat were omitted from the diet, than with hyposensitization injections alone. Twenty-two of these cases were observed through the pollen season corresponding to their skin sensitivity without pollen injections, while avoiding the other skin reacting allergen. Six (27 per cent), (3 by avoiding foods and 3 by avoiding foods and inhalants other than pollen), had such mild symptoms that pollen injections have not been warranted in subsequent years, and in 16, the avoidance of foods that induced nasal symptoms in the extrapollen season did not alter the severity of the hay fever. Of the 26 remaining cases, 10 have been under observation long enough to determine that hyposensitization injections, combined with food and inhalant avoidance, resulted in greater clinical relief than with only hyposensitization injections. In 4 of these, comfort has been maintained by food and inhalant avoidance alone after one to four years of combined treatment.

Table 2

HAY FEVER: 32 CASES

Skin sensitive	
To pollen and foods	17
To pollen, foods and other inhalants	14
To pollen—negative to foods	1
Therapeutic result by food and inhalant avoidance	
Satisfactory clinical result without pollen injections (3 P. and F., 3 P., F. and I.)	6
No influence on symptoms	16
Greater relief with combined treatment	10
One to four years' combined treatment, subsequently comfortable by food avoidance alone	4

P. and F., pollen and foods.
P., F. and I., pollen, foods and inhalants.

There are 23 cases of hay fever and bronchial asthma. All have positive cutaneous reactions to pollen; 12 also to foods, and 11 to foods and inhalants other than pollen. Three cases have been comfortable by food avoidance alone and the remaining 20 had symptoms of sufficient severity to require hyposensitization injections despite avoiding the other allergen. In 5 instances skin sensitivity was to seasonal foods, the ingestion of which induced nasal symptoms either at times when others similarly affected were having mild or no symptoms, or at a time when there was a very low concentration of pollen in the air, or when they were in a pollen free atmosphere. Because of the nature of the allergen, the deliberate feeding of these foods was impossible out of the pollen season. In the remaining 18 instances, foods induced either vasomotor rhinitis or bronchospasm, one or both, during the extrapollen season.

Table 3

HAY FEVER AND ASTHMA: 23 CASES

Skin sensitive	
To pollen and foods	12
To pollen, foods and other inhalants	11
Therapeutic result by food and inhalant avoidance	
Food avoidance, no other treatment, no symptoms, P. F.	3
Hyposensitization injections necessary despite avoiding food and other inhalants	20

P. F., skin sensitive to pollen and foods.

There are 81 cases of perennial vasomotor rhinitis, of which 74 gave positive skin tests; 30 of these to foods and inhalants other than pollen, 20 to foods, pollen and other inhalants, 18 to foods, 4 to foods and pollen, and 2 to inhalants. No positive tests were obtained in 6 instances, and in one instance dermographism

prevented accurate interpretation of the tests. Six of these cases, including the patient with dermographism, were clinically sensitive to foods and one to foods and inhalants. Of the 24 instances in which skin reactions were positive to pollen as well as to foods and inhalants other than pollen, 16 had no symptoms during the pollinating periods corresponding to the pollen giving the positive skin reactions, and 7 had symptoms at these times, thus transforming perennial into annual symptomatology. One case was not observed through the pollen season. Considering the group as a whole, there are 40 cases in which food is the dominant allergic factor; 18 in which food is the sole etiologic agent by skin and fed test, and 22 in which there is skin sensitivity to foods and inhalants, but in which food is considered the dominant factor because, upon its avoidance, exposure to the inhalant factor in low concentration failed to induce symptoms of sufficient severity to warrant hyposensitization injections. In the remaining 41, foods and inhalants were equally effective in producing nasal symptoms and the absolute avoidance of both was required for a good therapeutic result.

There are 26 cases of perennial vasomotor rhinitis and asthma; 19 of these gave positive skin reactions to foods, pollen and other inhalants; 5 to foods and inhalants other than pollen, and 2 gave no skin reactions. Of the 19 cases giving positive reactions to pollen as part of

Table 4

NONSEASONAL VASOMOTOR RHINITIS: 81 CASES

Skin Sensitive		Therapeutic Result by Food and Inhalant Avoidance		
		Foods Dominant	Foods and Inhalants Equally Effective	
To foods	18	18		
To inhalants other than pollen	2	1	1	
To foods and inhalants other than pollen	30	5	25	
To foods and pollen	4	4		
To foods, pollen and inhalants	20	6	14	Pollen 7; Other inhalants 6; Not observed through pollen season 1
No skin reactions	6	5	1	
Dermographism	1	1		
	81	40	41	

To foods and pollen	4	No symptoms during pollen season (10 F. D., 6 E. E.)	16
To foods, pollen and inhalants	20	Perennial to annual symptoms	7
		Not observed during pollen season	1

F. D., foods dominant.

E. E., equally effective.

Table 5

PERENNIAL VASOMOTOR RHINITIS AND ASTHMA: 26 CASES

Skin Sensitive		Therapeutic Results by Food and Inhalant Avoidance	
To foods, pollen and other inhalants	19	No symptoms during pollen season	8
		Perennial to annual symptomatology	11
To foods and inhalants	5	Foods dominant cause	2
		Foods and inhalants equally effective	3
No skin reactions	2	Foods dominant cause	2

Foods dominant cause	4
Foods and inhalants other than pollen equally effective in inducing symptoms	11
Foods, inhalants and pollen equally effective in inducing symptoms	11

their skin sensitization, 8 had no symptoms during the pollen season corresponding to their skin sensitivity while avoiding the foods and inhalants indicated by their cutaneous reactions, and in 11, perennial symptoms were transformed into annual symptoms by such restrictions. In the remaining 7 cases (which include the two with no cutaneous reactions in which foods were the cause), foods were the dominant factors in 4 instances, and in 3, inhalants other than pollen and foods were equally capable of inducing symptoms and the avoidance of both was required for a satisfactory clinical result.

There are 19 instances in which the chief complaint was other than nasal, but in which the clinical history disclosed that nasal symptoms were also present. In 7, the chief complaint was abdominal pain, in one case associated with purpura. In 6 others, it was headache, in one instance associated with purpura, abdominal pain and angio-edema. In 3 others, it was periarticular edema (the presenting symptom was "arthritis"), associated in two instances with angio-edema. In two others, it was colitis and there was one instance of impaired hearing. Five of these cases were skin sensitive only to foods, 12 to foods and inhalants, and two gave no cutaneous reactions. Clinically, food was the dominant causative agent for the presenting as well as the associated nasal symptom in 9 cases. In 10 cases, foods and inhalants were equally capable of inducing either the nasal or presenting symptom.

This group of patients, in whom clinical and not skin sensitivity furnished the criterion for selection, supplies in a small measure the opportunity to determine the influence of clinical food sensitivity upon the therapeutic outcome. In 59 (32 per cent), food was considered the dominant sensitivity because the avoidance of specific foods brought about a satisfactory therapeutic outcome. Of these, 40 had perennial vasomotor rhinitis; 9, allergic manifestations other than nasal; 4, perennial vasomotor rhinitis and asthma; 3 hay fever and asthma; and 3, hay fever. In 57 (32 per cent), foods and inhalants were equally effective in producing symptoms and the avoidance of both was necessary to produce a good therapeutic result without hyposensitization injections. Thirty-three of these were patients with perennial vasomotor rhinitis, 11 with perennial vasomotor rhinitis and asthma, 10 with allergic manifestations other than nasal, and 3 with hay fever. In 64 (36 per cent), pollen was determined to be one of the etiological factors by clinical observation and was considered the dominant factor because the avoidance of foods and inhalants other than pollen did not bring about a satisfactory therapeutic result. Twenty-six of these had hay fever; 20, hay fever and asthma; 11, vasomotor rhinitis and asthma; and 7, perennial vasomotor rhinitis.

The correlation of skin and clinical sensitivity in those giving positive reactions to pollen is aided by comparing them with others having symptoms due to pollen sensitivity and by daily pollen counts. Ninety-eight patients were skin sensitive to pollen, of whom 33 had no symptoms during the pollen season corresponding to their clinical sensitivity. Of the 64 who had symptoms during the pollen season, 26 had hay

Table 6

CHIEF COMPLAINT OTHER THAN NASAL: 19 CASES

Skin Sensitive				Therapeutic Result by Food and Inhalant Avoidance	
	S. N.	F.	F.I.	Foods Dominant	Equally Effective
Abdominal pain, inc. 1 associated purpura (7)		1	6	1	6
Headache, inc. 1 associated purpura, abdominal pain and angio-edema (6)	1	3	2	6	
Colitis (2)			2		2
Peri-articular edema (3)	1	1	1	2	1
Impaired hearing (1)			1		1
	—	—	—	—	—
	2	5	12	9	10

S. N., skin negative.
F., foods.
F. I., foods and inhalants.

fever; 20, hay fever and asthma; 11, perennial vasomotor rhinitis; and 7, perennial vasomotor rhinitis and asthma.

Table 7

COMPARISON OF SKIN AND CLINICAL SENSITIVITY TO POLLEN

	Skin Sensitive	Clinically Sensitive	No Symptoms During Pollen Season
Hay fever	32	26	6
Hay fever and asthma	23	20	3
Perennial V.M.R.*	24	7	16
Perennial V.M.R. and asthma	19	11	8
	98	64	33

*One case not observed through pollen season.

Because of the nature of the clinical sensitivity, it is impossible to make a similarly accurate comparison in patients with skin sensitivity to foods and inhalants other than pollen. Such patients routinely avoided contact with the usual etiologic inhalant factors and such other inhalant factors and foods as indicated by positive skin tests and dietetic diary. When they were free of symptoms, the clinical effect of the deliberate ingestion of the restricted foods as well as the effect of the deliberate or accidental exposure to the suspected inhalants were observed. In this manner, one was able to determine, not only the influence of foods in the production of nasal symptoms, but also the necessity for hyposensitization injections with the clinically effective inhalant. There were 57 such instances and none required hyposensitization injections; adequate comfort being obtained by careful avoidance of both the foods and the inhalants. These clinical observations illustrate the conception of total allergic dose, in that the avoidance of all clinical factors is necessary before complete relief is obtained, and the persistence, and perhaps the intensity of symptoms, depends upon the absorption of more than one clinically effective allergen. However, when pollen is part of the clinical sensitivity, one is less likely to obtain good therapeutic results at first by only the avoidance of foods and other inhalants. The addition of hyposensitization injections to these avoidances produces a better therapeutic result and subsequently, comfort may be maintained, in some, without injections.

Table 8

INFLUENCE OF CLINICAL FOOD SENSITIVITY UPON THE THERAPEUTIC RESULT

	Dominant Food Sensitivity	Foods and Non-Pollen Inhalants Equally Effective	Dominant Inhalants (Pollen)
Perennial V.M.R.*	40	33	7
Chief complaint other than nasal	9	10	
Perennial V.M.R. and asthma	4	11	11
Hay fever and asthma	3		20
Hay fever	3	3	26
	59	57†	64

*One case not observed through pollen season.

†Satisfactory therapeutic result without hyposensitization injections.

CONCLUSIONS

In patients clinically sensitive to foods:

(1) Multiple skin and clinical sensitivity is the rule rather than the exception.

(2) Skin sensitivity is not an unerring guide to clinical sensitivity.

(3) Skin sensitivity to pollen and inhalants other than pollen is not a command to treat with hyposensitization injections.

(4) The foods eaten most frequently are the ones most likely to induce allergic vasomotor rhinitis.

(5) Frequently food and inhalant avoidance is sufficient to bring about a satisfactory therapeutic result in perennial vasomotor rhinitis.

(6) In the instances of perennial vasomotor rhinitis, skin sensitive to pollen, avoidance of food and inhalants other than pollen usually brings about a satisfactory therapeutic result; but in some, the condition will be transformed into annual vasomotor rhinitis (hay fever).

(7) When bronchospasm complicates the allergic reaction in the nose, inhalants are more likely to be the dominant causative agents.

(8) Before determining that pollen injections are imperative, one should critically consider the clinical influence of foods and inhalants other than pollen. Observation through a season of pollination not infrequently will show that such injections are unnecessary, when other allergic factors are properly controlled. A few cases of hay fever are comfortable merely by food restrictions; others merely by avoiding specific foods and inhalants other than pollen.

(9) In many of these cases, it appears that the persistence and duration and, possibly, the initiation and intensity of symptoms depends upon the total allergic dose.

REFERENCES

1. Eyermann, C. H.: Food Allergy as the Cause of Nasal Symptoms. J.A.M.A., 13:91, 1928.
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DISCUSSION (*Abstract*)

Dr. Oscar Swineford, Jr., Charlottesville, Va.—Dr. Eyermann has presented an excellent supplement to his pioneer work in "Food Allergy as a Cause of Nasal Symptoms." If a destructive criticism were in order it would be that he confined himself too closely to the presentation of facts. However, his admirable unwillingness to generalize makes the task of the discussant much easier.

The food allergy in his 181 cases was discovered solely on the basis of skin tests and food diaries plus clinical verification. One wonders, naturally, how many more cases he could have included in this series had he resorted to Rowe's elimination diets, Vaughan's leukopenic indices, scratch and intradermal testing with more foods, and the detailed food history which we have found helpful.

The high percentage (20 per cent) of hay fever cases satisfactorily relieved by food and inhalant avoidances alone was a surprise. The number of cases helped by supplementing pollen desensitization with food and inhalant avoidances was not a surprise. That has been our impression for some time. This raises the question as to whether one should defer pollen therapy until the onset of symptoms in those who have avoidable "food and other inhalant" sensitizations, reserving co-seasonal treatment for those who may still need it. Dr. Eyermann's figures would suggest that one in five hay fever and one in eight asthma cases would have satisfactory results. When one considers that co-seasonal pollen therapy is satisfactory in about three out of five cases, there is certainly a reasonable doubt as to the wisdom of beginning pollen therapy as soon as the diagnosis of pollen allergy is made. More evidence must accumulate before this question can be answered.

While the figures presented show that food avoidance can increase tolerance to pollen, they do not show whether "other inhalant" avoidance, with or without hyposensitizing injections, can increase the tolerance for previously allergenic foods. Vaughan has pointed out what is now common knowledge, that perennial pollen therapy alone frequently relieves mild perennial respiratory symptoms. These observations suggest that prevention of the total allergic dose, by avoidance or by hyposensitization to either food, bacterial, inhalant or physical influences, should be reflected favorably in the management of any series of cases. In the individual it is still important, of course, to identify all clinically active allergens irrespective of their portals of entry or physical state.

Finally, the concept "total allergic dose" belies the false sense of adequacy engendered in the patient and subinformed physician by the diagnostic and therapeutic regimes currently promoted commercially. The promoters of these regimes would certainly increase their usefulness and lessen justified criticism if they would give adequate emphasis, first, to their limitations, and second, to the likelihood of satisfactory results from competent management when the commercial programs fail.

Dr. Eyermann (closing).—Whenever possible, patients with hay fever, skin sensitive to more than one genus, are observed through the pollen season corresponding to their skin sensitivity without pollen injections, while avoiding the other factors. Phylactic injections are used if the symptoms are severe notwithstanding.

I am inclined to believe, but it is difficult to prove, that food avoidance increases the tolerance for inhalants other than pollen. At least, some have told me that now, they could withstand the orris root present in crowds of women where formerly such contact induced symptoms; that it now requires several nights of contact with feather pillows before uncomfortable vasomotor rhinitis develops. I have only one individual sensitive to beef and horse dander, who is certain that horse dander is less effective in inducing symptoms when she is on a beef free diet.

FIBRINOUS PERICARDITIS FOLLOWING THYROIDECTOMY*

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The field of thyroid surgery is now a well explored realm, having been developed to its present state of perfection since Albucassis reputedly performed the first extirpation of the thyroid gland in the Tenth Century A.D. Despite the great frequency with which the operation has been performed, we have been unable to find in the literature any report of fibrinous pericarditis complicating the postoperative course of such patients; and, therefore, it seems well to record the fact that five such cases have come under our observation within the last two years. There has been no uniformity in the underlying indication for operation in these cases so the conclusion is warranted that it was the surgical procedure rather than the primary disease that was the precipitating factor. The first two instances of pericarditis occurred in young females with rheumatic heart disease who were subjected to ablation of the thyroid for the relief of cardiac insufficiency. This suggests that the operation may have caused a latent rheumatic process to become active, producing rheumatic pericarditis; however, our third case occurred in a woman with simple toxic goiter without any

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*From the Medical Service of The Sinai Hospital, Baltimore, Maryland.

evidence of rheumatic heart disease, an indication that our first hypothesis was not entirely correct. This was suggested also by the fourth case, a young man who had a simple cyst of the thyroid without any manifestation of hyperthyroidism. The final case of this series occurred in an individual with a combination of conditions, namely, hyperthyroidism and rheumatic heart disease.

No adequate explanation for the occurrence of this phenomenon has presented itself nor has there been opportunity to verify the clinically unmistakable signs of fibrinous pericarditis by postmortem examination since all the patients made complete recoveries and are well at the present time.

Case 1.—D. H., a 30-year-old Jewish girl, was admitted on May 25, 1935, and discharged December 8, 1935. Her complaint was dyspnea on exertion and recurrent edema of the ankles. She had had scarlet fever at the age of 5 years, but there was no history of inflammatory rheumatism, sore throat or chorea. She had been married for nine years and had one child twenty-one months old. For seven years prior to admission she had had symptoms of cardiac insufficiency with exertional dyspnea, orthopnea and repeated swelling of her ankles. These difficulties were all markedly exaggerated by her pregnancy two years previously. In 1934, she had a right-sided hemiplegia, which cleared slowly with practically complete return of motor function. For five weeks prior to hospitalization, she had been bedridden because of shortness of breath, palpitation, precordial pain, orthopnea, ankle edema, loss of appetite and a cough productive of blood-streaked sputum.

On admission, she presented the picture of early congestive failure with cardiac enlargement and the signs of both mitral stenosis and insufficiency and of aortic insufficiency. There was a slight enlargement of the liver but no edema of the ankles. The cardiac rhythm was totally irregular, but there was no deficit of the pulse at the wrist. Because of the patient's recurrent breaks in cardiac compensation and the gradually developing state of complete invalidism, ablation of the thyroid gland was considered a procedure which offered benefit. Her basal metabolic rate averaged plus 4 prior to operation. On October 3, 1935, under ether anesthesia, complete extirpation of the thyroid was done by Dr. G. C. Ney. The patient was returned from the operating room in good condition and ran the usual postoperative course except that on the morning following operation it was noted that a loud to-and-fro friction rub was present over the entire precordium synchronous with the heart sounds and totally independent of the respiratory murmur. This friction persisted during the day, but on the following morning, forty-eight hours postoperatively, there was only a slight friction audible in the diastolic phase of the cardiac cycle and this, too, disappeared within the course of the next twelve hours. The friction was very loud and leathery, but was unassociated with pain or any other significant clinical manifestation. The remaining period of the patient's stay in the hospital was characterized by the gradual development of surgical myxedema and this was controlled by the administration of small doses of thyroid extract. After leaving the hospital she was able to carry on her household duties in a manner that was impossible prior to operation and, although mildly myxedematous, she was certainly better off than she was before treatment.

Case 2.—R. R., a 33-year-old white woman admitted June 5, 1935, and discharged August 18, 1935, was first seen in this hospital in May, 1932, when a tonsillectomy was done. She had had acute inflammatory rheumatism ten years previously, when she was 20 years old. Following this attack she had been told that there was "something wrong with her heart." She was kept in bed during the latter half of her only pregnancy and was short of breath and had precordial pain and palpitation since that time. Following the tonsillectomy in 1932 she spent a large proportion of her time in bed because of severe exertional dyspnea when she was up and about. All her symptoms had grown gradually worse and she was sent to the hospital with the idea of having an ablation of the thyroid performed.

On admission she again presented all the classical signs of mitral stenosis and insufficiency which she had shown on her first admission. Her basal metabolic rate was plus 2 per cent. She had moderate pitting edema of the ankles and some hepatic engorgement with a few rales at the bases of both lungs. These signs of decompensation cleared up on bed rest and on June 26, 1935, Dr. G. C. Ney did a total removal of the thyroid gland under tribromethyl alcohol and ether anesthesia. She withstood the operation well, but in the afternoon of the day of operation she complained of precordial pain and a pericardial friction rub was noted just to the left of and over the lower portion of the sternum. This persisted for five days. At times the rub varied in intensity during respiration, but inasmuch as it was synchronous with the cardiac cycle, there was no doubt that is was pericardial and not pleural. The patient's further course was marred only by the development of temporary parathyroid tetany. Her basal metabolic rate came down to minus 17 prior to discharge. Since discharge she has been followed in the out-patient department and is able now to perform her household duties with very little difficulty.

Case 3.—E. S., a 40-year-old white female, was admitted November 14, 1935, and discharged July 13, 1936. She complained of a lump in her neck of one month's duration. Her past history was entirely negative. One year prior to admission her husband had been killed in an automobile accident and following this she has become increasingly nervous, particularly so in the preceding month, during which time she had noticed the appearance of a lump in her neck. Besides the nervousness she had become sensitive to warmth and felt hot practically all the time. For a month she had tired quickly, had cardiac palpitation and had made purposeless movements of her extremities. Although her appetite had been exceptionally good, she had lost thirty-five pounds in weight since her husband's death.

On examination she showed evidence of diffuse enlargement of the thyroid gland and moderate exophthalmos. There was marked tremor of the extended fingers. Blood pressure was 168/80. The pulse was 132 per minute and there was evidence of cardiac enlargement. Her basal metabolic rate was plus 73. After prolonged bed rest and attempts to bring the basal rate down with Lugol's solution, ligation of the superior thyroid artery was done on one side because medical measures had been without effect. Following this procedure she had a typical thyroid storm, during which she fibrillated

for some time. After some months of additional bed rest and iodine therapy, she left the hospital unimproved. One month later she returned for further treatment. On June 12, 1936, a right lobectomy was done by Dr. G. C. Ney under ether and tribomethyl alcohol anesthesia. From this operation she recovered without any complications and on June 26 the opposite lobe was removed. On the sixth postoperative day it was noted that a loud pericardial friction rub was heard over the precordium, loudest in the fourth left interspace. The rub was low-pitched, extended throughout both systole and diastole and was unrelated to respiratory movements. It had the typical grating quality of frictions associated with fibrinous pericarditis. The rub was persistent for the next six days, during which the patient had no precordial pain or any other symptoms associated with her heart. Her convalescence was otherwise uneventful and her basal metabolic rate came down to plus 7 with complete relief from all the symptoms which had brought her to the hospital. The pulse rate slowed from a rate of 120 to 90 and there was complete disappearance of the loud systolic murmur which had been heard over the precordium during the entire time that the patient had been under observation.

Case 4.—B. C., a 25-year-old white man admitted July 20, 1936, and discharged July 31, 1936, first presented himself to his physician complaining of a lump in his neck of one year's duration. For a period of a year he had noticed this mass in the lower anterior portion of his neck unassociated with any systemic manifestations.

On physical examination the thyroid gland was found to be enlarged on the left, moderately soft and slightly fluctuant. The trachea was deviated to the right. There was no exophthalmos, abnormality of the extraocular movements or tremor. The pulse rate was 80 per minute and the blood pressure 165/75. The heart was not enlarged and its rhythm was normal. A soft blowing systolic murmur was heard at the apex. There was no retromanubrial dullness and the thyroid could not be felt in the episternal notch. On the third day of his hospital stay Dr. Arthur Linde removed the left lobe of the thyroid gland under tribromethyl alcohol and ether anesthesia. At operation the right lobe and isthmus were found to be normal except for slight enlargement, but the left lobe was regularly enlarged to about the size of a small apple. The entire mass was tense, smooth, firm and salmon pink in color. No normal thyroid tissue could be seen. The entire mass was freed and easily removed from the external thyroid capsule. The patient withstood the operation well, but on the following day complained of epigastric pain, although examination of his abdomen and of his chest revealed nothing abnormal. However, his temperature was elevated to between 101 and 102°, and on the third postoperative day he began to complain of pain in the precordial region, at which time physical examination revealed the presence of a coarse leathery friction rub over the entire precordium. This rub extended through both phases of the cardiac cycle and was entirely independent of the respiratory murmur. It persisted for four days, becoming progressively louder during the first forty-eight hours and then gradually becoming fainter until it disappeared on the fourth day. With the disappearance of the friction rub there was a subsidence of the temperature and also of the precordial pain. The patient was discharged quite well eleven days after admission to the hospital.

Case 5.—B. N., a 27-year-old male, was admitted to the West Baltimore General Hospital* December 10, 1935, and discharged January 15, 1936. His complaint at that time was nervousness, fatigability and loss of weight since July, 1935. There was no previous history of rheumatic fever or chorea, and, in general, his past history was unrelated to his present illness. In July, 1935, he had noticed that he was perspiring more freely than usual and that he tired quickly. He had become nervous and quick of speech and action. There had been a loss of thirty pounds within five months. He also noticed that his eyes had become more prominent and that he had developed a tremor of his hands and fingers. He had diarrhea during the early part of his illness and for a month preceding admission he had had palpitation.

On admission to the hospital he had a temperature of 100.4° and a pulse rate of 120 per minute. His blood pressure was 142/76. There was marked exophthalmos, flushing of his skin, a positive von Grafe's sign, tenderness over the right frontal sinus, slight pyorrhea and a tendency to talk very rapidly. The thyroid gland was diffusely enlarged and the heart was enlarged to the left and there was an angry thrust felt at the point of maximum impulse in the fifth interspace. In addition to a systolic murmur there was a diastolic blow heard along the left sternal margin which had been noted for several months before the patient entered the hospital. The basal metabolic rate at that time averaged about plus 30. On December 17, 1935, Dr. Bertram M. Bernheim removed the right lobe of the thyroid gland under tribromethyl alcohol and ether anesthesia. At 4:00 p. m. on the afternoon of the first day a loud to-and-fro crunch was heard over the entire precordium synchronous with the heart sounds and independent of

*Permission to report this case was kindly given by Dr. Lawrence Katzenstein.

Table 1

SUMMARY OF CASES

Sex	Age	Diagnosis	Operation	Appearance of Friction	Duration	Symptoms
(1) D. H.—F.	30	Rheumatic heart disease	Ablation	24 hrs. p. o.	60 hours	None
(2) R. R.—F.	33	Rheumatic heart disease	Ablation	6 hrs. p. o.	5 days	Precordial pain
(3) E. S.—F.	40	Exophthalmic goiter	Partial lobectomy	6 days p. o.	6 days	None
(4) B. C.—M.	25	Cyst of thyroid	Partial lobectomy	3 days p. o.	4 days	Precordial pain
(5) B. N.—M.	27	Rheumatic heart disease and exophthalmic goiter	Ablation in 2 stages	9 hours p. o.	5 days	None

respiration. This gradually diminished over the left side of the precordium, remaining loudest to the right of the sternum. There was no increase in the area of cardiac dullness. On December 22, the friction was barely audible just to the right of the lower portion of the sternum and on the following day it disappeared altogether. The patient was discharged on January 15, 1936, having recovered from the operation, but not improved. The basal metabolic rate was elevated to plus 60 and all the signs of hyperthyroidism persisted.

He was admitted to the Sinai Hospital September 22, 1936, for removal of the remaining lobe of the gland. This was done on October 7, 1936, by Dr. William Rienhoff. Following the second operation there was no change whatsoever in the heart sounds and at no time was there any evidence of a pericardial friction, although careful observations were made with this in mind. He made a good recovery from the operation and improved rapidly so far as both the rheumatic heart disease and the hyperthyroidism were concerned. The only untoward events were a temporary paralysis of the vocal cords and parathyroid tetany, the latter controlled by the administration of calcium.

DISCUSSION

The problem of differential diagnosis at once suggests the possibility that these cases were the result of air entering the mediastinum through the operative wound. The occurrence of mediastinal emphysema following operations on the neck is a not infrequent happening and has been fully discussed by Graham,* who cites many references to this complication. There are some simple differential points which serve to distinguish this condition from that presented by the five patients reported above. The signs produced by air in the mediastinum are not entirely independent of respiration and have a very different quality from the rough, grating, continuous to-and-fro friction of fibrinous pericarditis. When mediastinal emphysema is present there may be subcutaneous air detectable by palpation. The sounds produced by air in the chest are of a "clicking" quality and may vary synchronously with the respiratory cycle. There was nothing unusual about the operative procedure in any of the cases which would lead to the suspicion that it was the result of surgical technic that the friction rub had occurred. In no case was there any substernal extension of the thyroid gland which would have led the surgeon to enter directly into the mediastinum. The usual precautions were taken to exclude air from the wound before closure was effected.

In no case was there any evidence that an intra-pulmonary or pleural lesion might be present. No pleural friction or rales were heard and there was no impairment of the percussion note. There was no cardiac enlargement beyond that which existed preoperatively. In the patients with rheumatic heart disease no progression of the endocardial or myocardial lesions took place so far as physical, electrocardiographic and roentgenologic examinations were concerned.

Following the disappearance of the friction rub there were no residua whatsoever; therefore, it seems apparent that the complication carries with it no malign prognostic import and is of interest to the clinician only insofar as it is an observation which has not hitherto been noted.

*Graham, E. A.: Surgical Diseases of the Chest, p. 192 f. f. Philadelphia: Lea & Febiger, 1935.

SUMMARY

(1) Five cases of fibrinous pericarditis following thyroidectomy are presented; two after total removal of the thyroid for the relief of rheumatic heart disease, one after subtotal thyroidectomy for exophthalmic goiter, one after partial lobectomy for removal of a simple cyst, and one after a first stage lobectomy in a patient with both rheumatic heart disease and hyperthyroidism.

(2) The absence of any adequate explanation for the appearance of this phenomenon is discussed and the points in differential diagnosis are presented.

THE TEACHING OF SYPHILIS TO UNDERGRADUATES AND POSTGRADUATES*

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In the past year great strides have been made in the syphilis control program initiated by the United States Public Health Service. It seems only logical that as momentum is gained the movement will go forward even more rapidly.

An intelligent public is showing an intense interest in the prevalence of syphilis and what can be done about it. There is reason to suspect that this interest among certain lay organizations exceeds that of the medical profession. An attempt, therefore, must be made to promote increased interest on the part of the medical profession and to encourage a more effective management of the syphilis problem than now exists. Two objectives in the education of the medical profession in syphilis present themselves.

*Read in Section on Medical Education, Southern Medical Association, Thirty-First Annual Meeting, New Orleans, Louisiana, November 30--December 1-2-3, 1937.

*From the Department of Medicine, Vanderbilt University School of Medicine, Nashville, Tennessee.

First, to care for the future we should insure the proper training of undergraduate medical students in the diagnosis, treatment and prevention of syphilis. It cannot be too strongly emphasized that this group of future physicians, in their formative stage, offer us the best material for the long-range attack on this disease and its multitudinous ramifications.

The second objective is the instruction of graduate physicians who are interested and willing to acquire more knowledge of the disease and anxious to assist in the immediate attack on the problem. This instruction is best carried out with postgraduates in residence at well organized clinics. However, postgraduate instruction by lectures and demonstrations at hospital staff meetings, county, district and state medical societies should not be lost sight of as a valuable method of arousing interest in the problem.

In the discussion of the objectives of teaching in the field of syphilis, I shall treat the subject from the point of view of the experience of the Syphilis Clinic of the Vanderbilt University Hospital. This Clinic has in the past (about 12 years) been mainly concerned with and active in the training of undergraduates in syphilis. Recently, as part of the program in syphilis control, the United States Public Health Service decided that opportunity should be given county health officers to spend a brief period of time in an established syphilis clinic. It appeared that the Syphilis Clinic of Vanderbilt University Hospital, having been established for years as a teaching clinic, should be a satisfactory one for the instruction of postgraduate physicians. This Clinic, aided by a grant from the United States Public Health Service, is therefore being expanded to undertake postgraduate instruction.

Before entering upon a discussion of the details of instruction in syphilis control, a short summary of the background of the Clinic is indicated.

The Syphilis Clinic of the Vanderbilt University Hospital was organized by Dr. Hugh J. Morgan as a special clinic of the Department of Medicine. As he[1] recently emphasized, both the pathologic and clinical aspects of this general infection, by their very nature, place it in the field of the internist. The staff of the Syphilis Clinic is therefore composed of men who have had training in the broad field of internal medicine. In fact, they spend more time in the teaching and practice of internal medicine than they do in syphilology. Knowledge in the broad field of medicine constitutes the natural foundation for special training in the problems of syphilis.

The Syphilis Clinic at Vanderbilt University Hospital is attended by about 350 patients a week in four clinic periods. A description of clinic personnel, organization and duties will introduce a discussion of teaching activities.

1. Morgan, Hugh J.: The Internist and the Syphilis Control Program. Ann. Int. Med., **11**:469 (Sept.) 1937.

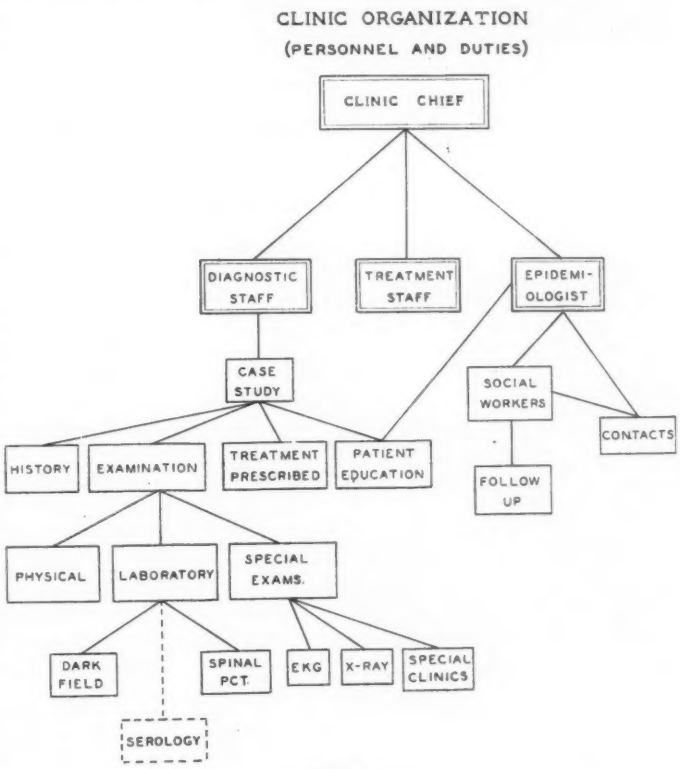

Diagram 1

The personnel may be divided according to duties (Diagram 1). Under the Chief of Clinic are: (1) the diagnostic staff, (2) physician in charge of treatment (treatment staff) and (3) epidemiologist.

The diagnostic staff consists of the clinic chief and six associates. The patients are first seen by a member of this staff and the case study carried out. This consists of history, physical examination and special studies, patient education and the prescription of treatment. A complete medical and venereal history are obtained. The physical examination is as complete as that carried out in the Medical Clinic. Darkfield and spinal puncture procedures are done in indicated cases. A technician is present for any laboratory procedures indicated. Though the serological laboratory is not under the jurisdiction of the Syphilis Clinic, its cooperation and collaboration are assured. "Special examinations" are included in the diagram to indicate that special diagnostic procedures, as electrocardiography, blood chemical examinations, roentgenography, are always available. Consultation with experts in the special clinics is always possible. From the viewpoint of teaching it is important that the Syphilis Clinic be a part of a polyclinic. The physicians on the diagnostic staff, having completed the general survey of the patient, are now in a position to determine the treatment indicated. They prescribe the drugs to be employed, indicating the dose and number of injections; they see the patient at intervals to follow the course of the disease and the effect of treatment; and they supervise in general the administration of the treatments. A further duty of this staff is to educate the patient. An explanation of the nature of the disease is given each patient together with a description of the plan of treatment which has been prescribed.

The treatment division is under the supervision of a physician, who sees that treatments are given exactly as prescribed by the staff of the diagnostic section.

The epidemiologist is a physician trained in medicine, syphilis and in public health. He is assisted by two full-time, trained social workers. This division of the Clinic carries on source and contact studies and maintains the "follow-up" of patients under treatment.

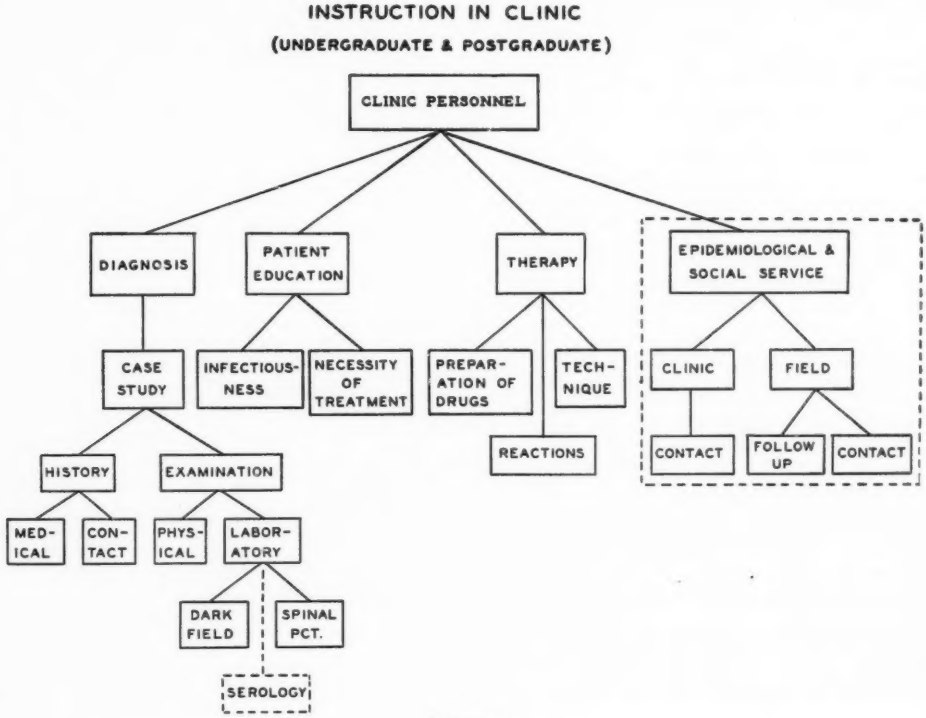

Diagram 2

In passing, it should be mentioned that research work is carried on in the Syphilis Clinic by certain members of the staff.

Instruction in the field of syphilis at Vanderbilt University School of Medicine is offered to the following groups: (1) undergraduate students, (2) Commonwealth fellows, (3) public health officers taking postgraduate work in Public Health, (4) public health officers in residence as postgraduate students in syphilis. Physicians in private practice are offered work similar to that outlined for the preceding groups. It is planned that instruction be available also for social workers and nurses.

The courses of instruction are planned to include four topics: diagnosis, treatment, patient education and epidemiology (see Diagram 2).

Case study, upon which the diagnosis rests, is placed in the hands of the student, whether undergraduate or postgraduate. He takes the history as related to syphilis as well as the general medical history, so that he may learn of symptoms due to complications of the disease or to the presence of other diseases. The history also includes all pertinent information relative to the source of the infection and subsequent contacts. Each case study includes a complete physical examination with all clothing removed from the patient. At the completion of these steps in the case study, one of the senior staff (always one having had five or more years of clinical experience) reviews the case with the student. The history is considered and further questioning carried out if necessary. Then the student's physical examination is adequately checked. The diagnosis is now discussed. If further studies (as darkfield examinations, chest fluoroscopy, and so on) are indicated, this is done under the instructor's direction. Arrangements are made for lumbar puncture at this time.

The next step in instruction is for the staff man to discuss with the patient the nature of his disease in the presence of the student. This is done so that the medical attendant may take his proper place in the education of the public relative to syphilis and its prevention. It is emphasized that syphilis is an infectious disease and should be discussed frankly and that it is not a disease to be mentioned only in whispers. The patient is disabused of the idea that he or she is being treated for a "blood disease" of indefinite or unknown cause. In acute cases the patient is instructed in regard to his infectiousness. To all patients is presented the need for treatment and facts relative to its duration. The dangers of inadequate treatment are emphasized. We believe this instruction of the patient is an extremely important function in teaching. Dissemination of knowledge will go far to develop a more rational attitude toward syphilis on the part of the laity.

During the time students are assigned to the treatment division they have an opportunity to observe the preparation of the various arsphenamines for intravenous treatments. Under the direction of the physician in charge of treatment the students learn the technic of veni-puncture for obtaining blood samples, the intravenous administration of drugs and the intramuscular injection of heavy metals. Immediate reactions to treatment may be observed.

The fourth division of instruction, and one of great interest to the postgraduate health officer, deals with the subject of the epidemiology of syphilis. This is an exceedingly important matter. Under the direction of the epidemiologist, assisted by two social workers, the student investigates the contacts of all new cases of syphilis admitted to the Clinic. During this period of instruction he spends much time in the field, searching out contacts for examination. "Follow-up" visits are also made to patients guilty of lapse in treatment, special attention being directed to those patients who failed to continue treatment while infectious.

The first three topics of instruction constitute those afforded undergraduate students in the Clinic. The epidemiologist activities are set off by broken lines in the diagram to indicate that they constitute a subject of especial interest to postgraduate health officers.

Opportunity is afforded to practically one-half of the fourth year class for instruction in syphilis. The course is an elective one of twelve weeks' duration. One-half of this time is spent in the diagnostic and the other in the treatment division of the Clinic. By this plan each student studies eighteen cases of syphilis, and has an opportunity to see, briefly, all of the material in the Clinic. He gives many injections of the arsphenamines and heavy metals. He has the opportunity to see numerous darkfield preparations of the *Treponema pallidum*. Though no provision is made in our plans for the undergraduate to devote time to field work and contact studies, it should be stated that students have case assignments for such work as part of their training in the Department of Preventive Medicine.

Health officers who take the general four months Postgraduate Course in Public Health at

the Vanderbilt University School of Medicine spend several hours in the Clinic. The Commonwealth Fellows (postgraduate students taking a four months general review course) also spend a few hours in the Syphilis Clinic where an attempt is made to stimulate interest in the disease.

Following the general plan of instruction outlined above postgraduate course in syphilis, designed especially for health officers, have been formulated. During a four weeks' course the health officer studies cases as does the undergraduate under the supervision of one of the staff members. Each trainee must familiarize himself with darkfield technic and learn to do lumbar punctures. A short time is spent in the treatment division of the Clinic. In the hours not spent in the Clinic the postgraduate health officer works in the field, locating contacts of the cases he has studied in the Clinic. A round table discussion each week allows for the consideration of clinical or epidemiological questions or problems which have arisen throughout the week. A series of lectures is provided the postgraduate covering the clinical and epidemiological aspects of syphilis.

DISCUSSION

The teaching plan used at Vanderbilt University Hospital Syphilis Clinic has been presented. It is our opinion that it offers the essentials necessary for the training of medical persons in a relatively short time.

For the successful consummation of the current campaign in syphilis control, present and future undergraduates must be stimulated to active participation. The stimulus is best provided by arousing in them interest in the many clinical aspects of the disease and its treatment. Education of the patient regarding the infectiousness of syphilis and his responsibility to prevent its spread are likewise of the greatest importance. If one-half of the fourth year students show enough interest to choose a course in syphilis, it seems certain that with proper instruction their interest will continue long after they have left the medical school.

Postgraduate training should provide the health officer with an intimate knowledge of syphilis. He must learn to study the individual patient. His problem is a person with syphilis and his or her contacts, and not merely a positive blood test to be made negative. A history and a physical examination must be included in each case study in order that treatment may be rational and treatment complications minimal. The darkfield examination should be made a part of the health officers' study of acute syphilis, for by early recognition and treatment of acute syphilis new infections will be prevented. The postgraduate must learn to interpret properly the serological reactions reported. Cerebrospinal fluid examinations are essential for the correct diagnosis and proper treatment of syphilis, and health officers undertaking the problem of syphilis control must be trained and equipped to perform lumbar punctures. Only by tracing contacts in the field will the student obtain practical training in the epidemiology of syphilis.

SUMMARY

In summary, Diagram 3 is presented. In this graph, we believe, are contained the practical elements of the syphilis control program. No teaching plan is complete unless it provides instruction in the principles of syphilis control as herein illustrated. Control of syphilis can be attained only if the patient is thought of as a link in a long chain of infections. Instruction must give this viewpoint: the patient to be studied, diagnosed, treated specifically, and instructed as to his disease; contacts to be found

ELEMENTS IN SYPHILIS CONTROL

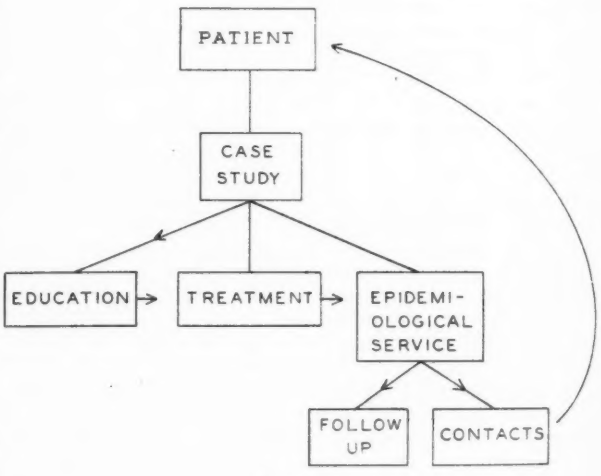

Diagram 3

and examined, keeping ever in mind the fact that contacts compose a group of potential patients with acute syphilis.

DISCUSSION (*Abstract*)

Dr. Seale Harris, Jr., Birmingham, Ala.—I do not fear contradiction when I state that the teaching of syphilis both to undergraduates and postgraduates at the Vanderbilt University School of Medicine is superior to that of most other institutions. I have personally visited a large number of medical schools and have been particularly interested in the teaching of syphilis. Nowhere have I seen a clinic conducted as well as at Vanderbilt. Unquestionably, the reason that this clinic is of such high type is that it is a part of the Department of Medicine.

Syphilis is a disease of the entire body and should not be taught as a part of dermatology, urology, or as an individual department. Undergraduate students should be impressed with the importance of considering syphilis as a medical and public health problem. Students who are instructed in finding the source of infection, the contacts of the infected person and the follow-up of patients are certainly better qualified to manage syphilis in practice.

During the last several years I have had the privilege of instructing postgraduate students in syphilis, and have had the opportunity of studying the problems which the practitioner meets. From this observation I have reached certain conclusions as to why syphilis is not being properly treated in this country at present. There are numerous reasons for this. However, I will mention only a few.

In the first place, it has been only recently that a more or less standardized plan of treatment for various forms of syphilis has been suggested. The United States Public Health Service and the Cooperative Clinical Group, which is made up of several of the leading syphilologists in the country, have formulated plans for the various forms of syphilis. These plans are now available to all physicians.

Another reason for the improper treatment of syphilis is the cost of the treatment to the patient. The fees charged the ordinary patient are more than he can afford to pay. I believe the fee for a treatment should be the same as for an office service.

A third reason for the inadequate treatment of syphilis is the patient's fear of treatment reactions. A great many of the reactions are due to improper preparation and administration of the drug. I would advocate the holding of numerous clinics at centralized points to which all physicians are invited. At these clinics proper technic could easily be demonstrated and many treatment reactions could be subsequently avoided.

One of Dr. Kampmeier's opening remarks was that the interest in syphilis among lay organizations might even exceed that of the medical profession. In this I heartily agree. I was present at a certain county medical society meeting not long ago. The ministers in this county had asked to be allowed to appear before the county society. They said that the organized churches of the county wished to offer their services to the county medical society in any way in which they might aid in the control of syphilis. The medical society, however, was not prepared to accept their aid because they had no definite program planned or arranged. I cite this as an example of the interest in lay organizations in the control of syphilis.

Syphilis is probably the greatest medical problem of today and the medical profession is more or less "on the spot" regarding its control. Only by proper undergraduate and postgraduate instruction can we hope to accomplish much toward its eradication.

Dr. W. S. Leathers, Nashville, Tenn.—The purpose of the syphilis clinic is primarily to teach undergraduate and postgraduate students. Therefore, it is necessary to organize this clinic on a careful basis so that the patient is not only given the best treatment in the clinic, but an investigation should be made also from an epidemiological standpoint. The personnel and facilities afforded for the operation of the Syphilis Clinic in the Vanderbilt Hospital make it possible to carry out this objective. The clinic has been organized in cooperation with the United States Public Health Service with the view of giving postgraduate instruction to health officers, physicians, specialists in syphilis, nurses, social service workers and undergraduate medical students.

Every patient who is registered in the clinic is given careful study, using the most modern methods for diagnosis and treatment. Laboratory examination is made from time to time under the direction of a clinician so that the progress made in treatment can be intelligently interpreted. The records are being kept so that the patients are classified from the standpoint of analyzing the results achieved with reference to arresting or curing the disease. In a word, the problem is approached not only from the standpoint of a treatment center, but also with reference to the significance of the disease in the community. Patients are advised with reference to their contacts and, as far as is practicable, educational measures are continually emphasized.

Dr. Kampmeier (closing).—I believe that Dr. Harris is correct regarding the matter of the fee charged by private practitioners. Too often the physician's attitude is that, since a venereal disease is being treated, the patient should be charged a fee out of proportion to other services rendered.

Dr. Leathers mentioned the preventive and epidemiological aspects of the syphilis problem. In the recent intensive attack we have made on this phase, it has been interesting and gratifying to see the progress. Though this has been going on only a few months, I feel that time will show remarkable results.

MODERN MEDICAL EDUCATION AS IT APPLIES TO UROLOGY*

By HAMILTON W. MCKAY, M.D.
Charlotte, North Carolina

The title of this address selected by me will prove a surprise, I feel sure, to many of my friends. Wherefore, please pardon a personal reference by way of explanation. Your Chairman is one of those restless people who is happiest when acquiring, organizing or building up new knowledge. What is education if it is not building? Surely it is an old story: dissatisfaction with one's own attainments, educational or otherwise. In the field of athletics, for instance, such dissatisfaction is often illustrated: we see an athlete excelling in one position, but wanting to play another. "Ty" Cobb, one of baseball's great outfielders, always longed to be a pitcher; those of you who are baseball fans will remember seeing him "warm up" before a game, almost injuring his arm as a pitcher instead of practicing his own position. Jack Dempsey had his face lifted in an endeavor to become a movie actor; Gene Tunney yearned to be a poet instead of a prize fighter. I have always wanted to teach medicine, but opportunity knocked at my door only once, and passed on. However, my chief interest has been and always will be in medical education.

The point of view expressed in this address is that of the active practitioner rather than that of the teacher. Many other observations have been made during membership on the Board of Medical Examiners of North Carolina.

Consideration of a subject dealing with the education and training of the present day specialist demands first of all a brief discussion of the recent trends and changes in medical education, and of the basic qualifications entering into the selection of the modern medical student. One essential upon which we unanimously agree is that, in order to have better physicians, we must have a more careful individual selection of our medical students; to give the people better specialists, we must first have physicians who have had better general training before becoming eligible to apply for training as specialists. It should be a basic requirement that the candidate for a specialty should have training equal to or the equivalent of a rotating internship of two years in a good hospital. Having met this requirement, the specialist should be as carefully selected upon an individual basis as is the medical student.

In discussing medical education in its literal sense, we must recognize that uniform standards of training and licensure are comparatively new in our country. Only about thirty years ago many of our medical schools were commercial institutions and had few uniform requirements. A study of the state boards of licensure shows that in 1904 few of our medical colleges had any entrance requirements, and only ten states required graduation from high school. A sincere desire to protect people from poorly trained and unqualified physicians has brought about rapid and radical changes in medical education in the past three decades. Such changes have led us to believe that medical education is governed by the same principles as other branches of education, except that medicine involves greater responsibility and a deeper obligation to the individual and to society as a whole. Dr. Willard C. Rappleye[1] writes:

> "The premedical student, the medical student, the intern, the hospital resident, the general practitioner, the specialist, and the public health administrator, all are, from the educational point of view, merely different phases in training of personnel for the care of the sick and the preservation of health."

Medical education is and always will be dependent upon general education.

Time does not permit me to discuss premedical training except as it applies basically to all specialties. The selection of the student for the study of medicine must be made on an individual basis, preferably through a personal interview with the dean or one of his representatives. In no business or profession are the basic qualifications of character, honesty of purpose, and personality so essential in the raw material as they are in the premedical student. After all, in their broadest conception, medical education and hospital training are no more and no less than the preparation of a cultured expert who is a gentleman, not only in name, but in truth. Too many doctors work as though they were merely trained technicians; we forget that there is no substitute for gentlemanly culture in medicine.

During the past five years as a member of the Board of Medical Examiners of my state I have heard much concerning the great number of doctors who apply for admission to medical practice in North Carolina. Should the large quota of medical students cause wonder, we have

*Chairman's Address, Section on Urology, Southern Medical Association, Thirty-First Annual Meeting, New Orleans, Louisiana, November 30--December 1-2-3, 1937.

only to remember that the number of graduates from our institutions of higher learning has increased eight times as rapidly as the population during the past forty years. My only excuse for mentioning numbers at all is to emphasize the fact that what the country needs is better doctors and better specialists, not necessarily more of them. One of our greatest needs is that of adequate facilities and opportunities for those already in practice to do postgraduate study.

A requirement of all national and state boards of licensure should be that the candidate applying for a license must spend a specified amount of time each year in postgraduate study. Every physician should be required to serve an internship before he or she is granted the M.D. degree. This internship should be a part of the unit of undergraduate training, and should be preferably a rotating service given in another hospital under instructors others than the student's regular teachers.

Training of interns, except in a few institutions, is far from ideal. The intern is now trained with undue emphasis upon promotion to the next highest position on the house-staff, instead of being consistently impressed with the importance of his future obligation and duty to the public. The story of the three stone-masons should be told many times to every intern for his inspiration. This is the story. Three stone-masons were chiseling stone on a mountain side. A passing traveler paused and asked Mason A what he was doing. He replied, "I am chiseling stone." To Mason B, the same question was put, and the same answer given. But when the traveler asked Mason C what he was doing, the man rose and declared, "Sir, I am building a cathedral."

The modern teaching hospital is literally "cluttered up" with interns, one passing instruments, another doing dressing, neither inspired with the fact that he is being tutored for a life work of great responsibility requiring continual study and many sacrifices. How deplorably little are our interns taught about the social, economic and psychological aspects of medical care!

I have spent more than the allotted time in discussing premedical education, undergraduate education, the training of the intern. Why? Because it is impossible to discuss the training of the urologist without first being assured that he has been properly selected as a medical student, culturally prepared to study medicine, and, most important of all, taught and inspired as an intern with a keen realization that his chief purpose in life is to prepare for later usefulness in solving the great problem of better health.

We now assume that the medical graduate, during his undergraduate training and internship, has seen and examined a sufficient number of patients and of specimens to be able to correlate symptoms and pathology; that by means of careful observation he is able to recognize, as Dr. Dean Lewis[5] puts it, "the face of disease." The doctor, in order to specialize, should know the face of disease and be able to recognize it as he would that of an old friend. The training of specialists, particularly of urologists, is the special problem with which this paper is concerned. Is it not remarkable that only five urologists[2 3 4 6 7] have written on the teaching of urology?

The preparation of any specialist naturally divides itself into two aspects: undergraduate training and graduate training. In preparing undergraduates for specialization in urology, medical faculties might well consider the following suggested basic course in urology and venerology, with a minimal required course during the third year, and an elective course for students especially interested in the subject during the fourth year. I believe that a required course should cover the following subjects, as suggested by Dr. Quinby:[7 8]

(1) Review of anatomy, embryology and physiology of the genito-urinary organs

(2) Pathologic physiology of the genito-urinary organs.

(3) Elementary examination of external genitalia and diagnostic procedures

(4) Injuries to the urinary tract

(5) Infections

(6) Urogenital tuberculosis

(7) Stone formation

(8) New growths, including hypertrophy of the prostate

(9) Required venerology during the third year, based on the revised course at the University of Pennsylvania introduced by Dr. John H. Stokes.[10]

In addition, there should be two consecutive clinical teaching hours each week of one semester. Four hours a week of practical work for six weeks should be required of every member of the third year class. In the teaching section the student should personally witness or actually collect the material for demonstrations of

the Treponema pallidum, the gonococcus, and examination of urine (shreds, and so on). He should learn to draw blood, and the technic and importance of the complement fixation tests. He should be taught the proper methods of intramuscular and intravenous injections.

This type of instruction is best given in the out-patient department, and should be supplemented by having the student examine the patient and demonstrate him to the section or class. This actual contact of student and patient must be carefully supervised, and the teaching augmented by modern instruction methods such as slides, moving pictures, models, drawings and other means that will indelibly impress upon his mind the diagnosis and prevention of urological diseases.

Basic facts about sex education and prevention of venereal disease must become an integral part of every urological student's fundamental knowledge. He should be taught early that he has a duty to the community and to the nation in, first, knowing how to give instruction about prevention of gonorrhea and syphilis; then applying this knowledge when he shall have been graduated into practice.

The elective course can best be given in the fourth year. Such a course would probably attract one out of five to eight students. This course should be, in a broad sense, complete enough to give the interested student specialist a thorough foundation in urology and venerology on which to build. We should find the senior student assuming care of the patient, studying the cause of the disease, and learning about its treatment. In this course the student must be in turn adviser, diagnostician, therapist and friend. He must prove himself a cooperating and intelligent individual in the specialty in which he has elected to major.

If this kind of carefully supervised teaching was carried out, it would not be so difficult to select men who want to specialize after completion of their internship. Such instruction would tend to prepare the specialist, just as a broad cultural education prepares the medical student.

To build high, a strong foundation is necessary.

As to our second aspect of preparation of the specialist, graduate teaching, the modern hospital certified for the training of interns usually offers a medical or surgical service. The result is that the human product of such an institution can do only one thing well. If he is a hospital graduate in medicine, he knows how to examine a chest; if he has had a surgical service, he can open the belly. He knows little about making a decent rectal or vaginal examination, and does not know conjunctivitis from iritis. He does not know otitis media from a furuncle in the auditory canal. He would faint if asked to give an anesthetic. The training of an intern should amount to preparing an all-round doctor with the humanities of medicine drilled into him. If he wants to specialize, he must pay the price of more time and effort.

In teaching the intern urology, a general rotating service of two to three years, or the equivalent in general medical and surgical experience, is necessary as a basic requirement. In such general preparation we cannot hope to give the intern more than a point of view. He is taught how to get diagnostic evidence and how to correlate symptoms and pathology. In other words, he should know how to recognize the face of urological diseases.

The laboratory has been to him a place for obtaining much important evidence to complete certain opinions. The operating room has so far been a laboratory for proving or disproving his diagnosis. The bedside study of his patient should stand out as the most important single event in the study of his case. If the young would-be urologist does not realize what bedside diagnosis means, and if he cannot experience the thrill of recognizing the face of some rare disease as he would that of an old friend, such a young urologist is doomed to be a technician or a plumber.

Now our intern in a urological institute or on a large, well organized urological service, has at last reached the final gate to the goal he has been seeking. Here he begins to learn the technic peculiar to his specialty, the details of diagnosis, care and treatment of urologic diseases. Through assisting with the more complex procedures and doing the simpler ones himself, he becomes increasingly familiar with the information elicited and its interpretation. As first or second assistant at operations he sees revealed the proof of the value of the often tedious work-up of his cases.

For graduate training of the finished urological surgeon who has had the necessary rotating service, selection of candidates is at present not rigid enough. This selection should be based on actual record of the candidate as a student who majored in urology and as a rotating intern: on his general outlook on things social and economic; on his psychological reactions: on his

character, his enthusiasm for urology, and his personality.

The following regime constitutes the ideal training in urology for the hospital-trained man:

(1) A three years' rotating internship, with third year major in general surgery, or rotating surgical specialties of four months each.

(2) Intern in urology for one year.

(3) Assistant resident in urology for one year.

(4) Resident in urology for one year.

I regard it as most important that at some time during his three years the young urologist act as office assistant to a practicing urologist for at least six months.

Postgraduate urological training for physicians who have been in general practice for some time may be divided into a diagnostic or a standard course. Neither of these courses should be given to any matriculants except a select group of hospital graduates. The intensive practical six months' course as given at the New York Post-Graduate Hospital under the direction of Dr. McCarthy,[6] certainly has a place in the sphere of postgraduate teaching in urology. Surely it is dogmatic to state that a selected doctor, graduate of a grade A medical school, with an internship of from two to three years, cannot, or is not fit, to begin the study of urology by an intensive six months' course of seven hours a day. If he has been selected wisely, this type of doctor could acquire the fundamentals of diagnostic urology. He might be graduated as a diagnostic urologist and in subsequent years complete his surgical training.

Courses of from six weeks to three months in cystoscopic and urological diagnosis are advocated by Dr. Roger Barnes[1] of Los Angeles for general practitioners in smaller communities where the general public does not have ready access to the services of a specialist in urology. Thus patients with major urological problems may be detected and referred to larger centers for special urological treatment.

A member of this second group of postgraduates should spend two and a half to three years in intensive study as resident or assistant in urologic surgery before he can qualify as a urologic surgeon. Another way in which the mature student, whether he is doing graduate, or particularly postgraduate work in urology, may keep abreast of the times is by attending organized urological meetings where often he may learn as much as through a week or ten days of intensive postgraduate study. Also, yearly attendance at clinics is valuable in giving the trained man new ideas, recent information about technic, new instruments, and so on.

Finally, I ask that you give serious thought to teaching and training of the 1937-38 model urologist. I hope that someone along the long road of training reminds him that urology is an art as well as a science and that it is essential that he first become a clinical diagnostician, then surgeon, and finally urologist.

CONCLUSIONS

In conclusion, may I summarize my feelings in regard to medical education and urology as follows:

(1) A physician with proper character, suitable mental attainments, and correct basic training should not be denied the right to specialize on account of dogmatic formulae or lack of funds.

(2) Every specialist should have a well planned, well organized rotating hospital experience of two to three years or its equivalent.

(3) The grading organizations should consider certification of urologists of two classes: diagnostic urologists, and urologic surgeons.

(4) More careful selection of graduate and postgraduate candidates for the study of urology would insure protection of the profession and the public.

(5) More attention must be given to postgraduate medical education in order that great endowments may be secured.

(6) Properly endowed medical schools and hospitals should be provided for postgraduate teaching in order to solve the proper selection of the specialist already in practice.

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Volume 31 FEBRUARY 1938 Number 2

EDITORIAL DEPARTMENT

SOUTHERN MEDICAL ASSOCIATION
Thirty-Second Annual Meeting
Oklahoma City, Oklahoma, November 15-18, 1938

MEDICAL CARE FOR THE DESTITUTE

The subject of medical compensation for services to low income groups of the population is said to be less burning, less ready for explosion, in the South than in any other part of the Union. To permit free discussion of economic problems by physicians, Dr. Harvey F. Garrison, of Jackson, Mississippi, Councilor of the Southern Medical Association, and recently President of the Mississippi State Medical Association, two years ago inaugurated a meeting of presidents and officers of state medical societies, to be held during the Southern Medical Association's annual meetings. The two meetings which have resulted have been well attended and most enlightening. In his able address before this group in New Orleans in December, Dr. Garrison expressed the feeling of a majority of practicing physicians in his condemnation of government-controlled health insurance programs now operating in England, France, Germany and other foreign countries. Dr. Garrison added:

"The threat of a nationally controlled plan of health insurance is at our door. Any attempt to encourage the lay population of this country in the belief that the care of its health is largely the function and responsibility of the government is pernicious, dangerous, and obstructive to progress."

In the past few years the government has undertaken the feeding of a huge group of the population. A population which cannot feed itself obviously cannot pay doctors' bills. According to social service agencies many persons on relief could become self-supporting if they had medical attention.

There have been put in operation in the past year in several states programs for the provision of medical aid to indigent families by government supervised cooperative plans. The Board of Censors of the Medical Association of the State of Alabama has just approved a program providing medical attention for certain destitute families in rural communities. It is typical of other projects being undertaken.

Certain families under the Federal Resettlement Administration are to be established on farms. The families under consideration have average total assets of $3.05. The program is to lend them funds for a year's necessities: food, clothing, and shelter, agricultural implements, live stock, seed, fertilizer, and medical care. Ordinarily they could pay nothing for a physician's services. Under the arrangement authorized they are to pay a maximum of twenty-five dollars per year per family, less in some states, this to cover home and office visits of the physician, simple drugs and obstetrical care, not surgical operations or hospitalization. The county medical societies are to be asked to furnish a list of physicians willing to undertake this work and the patient is to be permitted free choice from the list. The physician will thus receive a small compensation for a year's services to families which would otherwise be charity patients.

There are approximately ten thousand families under the rural rehabilitation division of the Resettlement Administration in Alabama, distributed through every county but one. Government, in rehabilitating them, prepares a budget for each and supervises its expenditure. It specifies exactly how much lard, bacon, lean meat, meal, flour, sugar, jam, coffee, molasses, soda and spice, tobacco, how many overalls,

socks, undergarments and what medical care each family should purchase.

Physicians are told that their compensation is obviously inadequate, but that neither do these families receive as much food or clothing as they need; that the medical services should be proportionate to the standard for other necessities. The difficulty here is that the physician usually knows how to practice only one variety of medicine. Its quality cannot be strained. This fact may tempt self-sustaining neighbors of families in the rural rehabilitation program to demand a similar type of service.

The aim of the program, however, is to lift these destitute families into the class which owns property, is able to purchase its own provisions, and pay its own medical bills. If the project is successful, it should eliminate itself or greatly curtail its activities in the course of a few years instead of expanding. The experiments in rehabilitation and in distribution of medical care will be watched with much interest by the country at large.

PITUITARY AND THYROID

The thyroid, the site of many surgical operations, is clinically the first recognized and best understood endocrine. The approach to the pituitary is so difficult that this gland in the human is not often attacked with the knife. However, pituitary hypertrophy is probably not rare. Various suggestions have been made in recent years as to indications and methods for irradiating it; and it is readily removed surgically from small animals, with a low operative mortality. Irradiation of the pituitary has been suggested for various conditions, including rapid growth of children. A rate of more than two inches per year has been offered as an indication.[1] Its physiologic effects extend into all portions of the body and have offered a rapidly expanding field for investigation by clinicians.

The thyroid has been demonstrated to contain only one active secretion. The adrenals and pancreas have yielded two each; the gonads two for each sex, but the hormones of the pituitary have become legion. At the turn of the century a secretion of the posterior lobe was isolated, which has since been continuously employed by obstetricians and surgeons. The next pituitary hormone was postulated in 1912, a growth hormone, when Cushing and Davidoff described the syndrome of acromegaly and produced experimental gigantism in dogs. In more recent years the pituitary has yielded extracts which stimulate ovaries and testes; these are the gonadotropic hormones. Diabetogenic and lactogenic extracts from this gland have been reported, which cause increase of blood sugar and secretion of milk. These might be called pancreatropic and mammotropic hormones. Adrenotropic and thyrotropic materials have also been described. Specific extracts have thus been reported from the anterior pituitary lobe which cause hyperplasia and increased physiologic activity of gonads, pancreas, mammae, adrenals and thyroid.

Chemical, physiologic and histologic findings in the pituitary have been very interestingly correlated. The appearance of the normal gland, with its basophil, acidophil and chromophobe cells has long been known. The basophils are generally believed to secrete the sex hormones and the acidophils the growth hormone. Characteristic changes have been described in pregnancy and after castration. After castration the gland accumulates a considerable excess of gonad-stimulating hormone, which is perhaps difficult to dispose of in the absence of ovaries and testes. Castrate cells appear, which are large and base staining.

One might expect that thyroidectomy would cause an accumulation of thyrotropic hormone in the gland, with increase of the cells which usually secrete the thyroid stimulator. This has been reported and also disputed. Zeckwer, of the University of Pennsylvania, has recently investigated the hypothesis rather extensively. There is, of course, a general dwarfing of the young rat after thyroidectomy, with the development of cretinism; at the same time the weight of the pituitary is relatively increased. The cretin pituitaries have also, for the size of the animal, a considerably increased quantity of thyrotropic hormone which may be demonstrated by injecting cretin pituitaries into normal guinea-pigs.[2] They quickly stimulate the guinea-pig thyroid. This reaction, of increase of thyrotropic hormone in the pituitary after thyroidectomy, would parallel that of the commonly observed increase of gonad-stimulating hormone after castration.

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1. Engelbach, William: Endocrine Medicine. Springfield: Charles Thomas, 1932.

2. Zeckwer, Isolde T.: Thyrotropic Effect of Pituitaries from Cretin Rats. Amer. Jour. Physiol., **117**:518, 1936.

Following thyroidectomy in rats, according to Zeckwer,[3] histologic changes in the pituitary are as striking and as characteristic as those after castration. There is a great accumulation of hyaline material in the basophilic cells, and the loss of acidophilic cells is quite notable. The histologic appearance of the cretin pituitary and the castrate pituitary superficially resemble one another, and have caused considerable confusion and argument among investigators. If the young rat is both castrated and thyroidectomized, according to Zeckwer, the difference between the thyroidectomy cells and castration cells of the pituitary may be readily seen. Castration cells are large with deep blue staining coarse granules. The thyroidectomy cells have fine granules and the color is possibly in the cytoplasm. Castration cells appear with no decrease in the number of acidophils, but the production of thyroidectomy cells is at the expense of the acidophils, the loss of which is striking. In certain pituitaries after thyroidectomy almost every acidophil disappears; in others there is conspicuous degranulation. The loss of acidophils is associated with dwarfing of the animal and is a rough quantitative indication of its extent. This is in accord with the belief that the acidophils secrete the growth stimulating hormone; also that this hormone acts chiefly through the thyroid.

Since the pituitary undergoes a characteristic histologic change after castration and after thyroidectomy, furnishing typical hypogonad and hypothyroid pictures, one would expect to find also opposite effects in cases of hypergonadism and hyperthyroidism. Continued injections of theelin, or administration of thyroid extract should be reflected in the cells of the pituitary. Pituitary tumors in rats have been produced by this means.[4] In hyperthyroidism one would expect an increase of acidophils. Necropsy studies of the human pituitary after thyroidectomy, for example after thyroidectomy for angina pectoris, would be of interest.

Irradiation or extirpation of the human pituitary, of course, could not act selectively upon one type of its cells, or diminish only one of the many secretions of this complex gland. Operation upon it or irradiation would destroy the source not of one but of many essential internal secretions.

3. Zeckwer, Isolde T.: Morphological Changes in Pituitaries of Rats Resulting from Combined Thyroidectomy and Gonadectomy. Amer. Jour. Path., **13**:985 (Nov.) 1937.

4. Zondek: Tumor of the Pituitary Induced with Follicular Hormone. Lancet, **1**:776-8, 1936.

GLEANINGS FROM RECENT JOURNALS

The Urine in Nephritis.—One would not expect to learn a great deal from study of the specific gravities and acidities of ten thousand urines, yet Ziegler and Brice,[1] in San Francisco, have made interesting observations on this seemingly outworn subject.

They report a close relation between acidity and specific gravity. Nearly 90 per cent of all specimens voided were acid. Approximately 3 per cent were neutral and 9 per cent alkaline. The average specific gravity of the acid urines was 1.0196; of the neutral 1.0141; and of the alkaline 1.0127. Acid urines thus had a notably higher specific gravity. The calculated solid output for acid urine is very much higher than for neutral or alkaline. Acid urine, these workers conclude, is a much more efficient medium for excretion of waste products. In fatal uremia they note that the urine is often alkaline. Alkalis, as commonly employed in the treatment of nephritis, may have a temporarily beneficial effect in dissolving casts which block the kidney tubules, but when used for any length of time, as they are by both laymen and physicians, they interfere with excretion and may cause kidney injury.

There is no more reason, according to Ziegler and Brice, why sodium bicarbonate should be a household remedy than for hydrochloric acid to be kept on the family shelf and drunk *ad libitum.*

Benzedrine and the I. Q.—It was formerly believed that the intelligence quotient was a fixed ratio, which remained the same from birth and could not be improved by any individual effort or outside influence. With the widespread employment of intelligence tests in the public schools from year to year, this has been proven a fallacy. The intelligence quotient may deteriorate or even increase with age.

Drugs may affect the score. Bradley,[1] of Rhode Island, administered benzedrine to a group of children of normal intelligence, and reports a great increase in their interest in school work and in the drive to complete the usual tasks. Both comprehension and accuracy were increased, but the improvement disappeared as soon as daily administration of the

1. Ziegler, Edwin; and Brice, A. T.: Reaction and Specific Gravity of Urine in Relation to Nephritis: A Study of 10,000 Urinalyses. Ann. Int. Med., **11**:768 (Nov.) 1937.

2. Bradley, Charles: Behavior of Children Receiving Benzedrine. Amer. Jour. Psychiat., **94**:577 (Nov.) 1937.

drug was stopped. Some of the children were stimulated, some were emotionally depressed by the drug.

Molitch and Eccles[1] studied the effects of benzedrine upon the intelligence quotients of children. Half their group received a placebo; all the intelligence tests improved, but greater improvement was observed after benzedrine. More nervousness was reported after the placebo. Apparently some temporary quickening of thought processes occurred after benzedrine.

It is to be hoped that students preparing for examinations will not take too readily to this drug, and thus falsify the records.

Vitamin D and Height.—Vitamin D not only prevents bow legs, but adds something to leg length. Workers[2] in Detroit have recently analyzed the effect of this accessory dietary factor upon five hundred infants of the indigent or near indigent class over a period of years. Vitamin D was given as irradiated evaporated milk or in cod liver oil, other dietary factors being adequate.

Linear growth in the first year of life was observed to be closely related to the D intake. Infants in low D groups, even those above the rachitic level, both male and female, were shorter than infants who consistently received a larger D allowance. Six hundred units per day seemed to be the optimum amount. Greater linear growth was not obtained in infants who received more vitamin than this. The greatest increase in height was obtained if the vitamin was administered before the age of eight months.

The work confirms studies reported in 1936 on the same subject. Vitamin D would seem to be an important factor in the increased height of the present day child.

1. Molitch, Matthew; and Eccles, A. K.: The Effect of Benzedrine Sulfate on the Intelligence of Children. Ibid, p. 587.
2. Seyker, F.; Hamil, B. M.; Poole, M. W.; Cooley, T. B.; and Macy, I. G.: Relationship Between Vitamin D Intake and Linear Growth in Infants. Proc. Soc. Exper. Biol. & Med., **37**: 499 (Dec.) 1937.

Book Reviews

Physical Therapy in Arthritis. By Frank Hammond Krusen, M.D., Associate Professor of Physical Medicine, The Mayo Foundation, University of Minnesota; Head of the Section on Physical Therapy, The Mayo Clinic. Foreword by Melvin S. Henderson, M.D. 180 pages, illustrated. New York: Paul B. Hoeber, Inc., 1937. Cloth $2.25.

Emphasis is given this very important phase of treatment of arthritis by one qualified through long experience. The fundamental agents used, as heat, cold, massage, manipulation, exercise, rest, are so clearly presented that any one interested in the subject will find this book most helpful. The condition of fibrositis is adequately discussed with many helpful suggestions as to its treatment. Attention is called to the often overlooked simple measure of proper shoe fitting with corrective appliances.

Psychiatric Nursing. By William S. Sadler, M.D., Chief Psychiatrist and Director, The Chicago Institute of Research and Diagnosis; Consulting Psychiatrist to Columbus Hospital in collaboration with Lena K. Sadler, M.D., Associate Director, The Chicago Institute of Research and Diagnosis; Medical Director, the North Side Rest Home; Attending Physician, Columbus Hospital and the Women and Children's Hospital, and Anna B. Kellogg, R.N., Member American Nurses' Association; Chief of Nurses, the Psychiatric Clinic of the Chicago Institute of Research and Diagnosis; Instructor in Psychiatric Nursing, the North Side Rest Home. 433 pages. St. Louis: The C. V. Mosby Company, 1937. Cloth $2.75.

The practice of psychiatry is no longer confined within the walls of an institution. Coincident with this transition, the need for a nurse possessed of more brawn than brain has changed to a demand for individuals possessing kindly dispositions, discriminating minds and reasonably keen powers of observation, based on an elementary, but none the less accurate, understanding of mental mechanisms.

This book is written to meet the increasing demand for psychiatric training for nurses. It represents a condensed version of the author's large textbook of psychiatry revised to include sections on nursing care. The chapters on occupational and physical therapy are a valuable addition to the text. The section on the psychiatric nurse should be carefully read by all nurses.

For the purpose of an elementary introduction to the subject, it is inclusive and clearly written, but I fear the average nurse will be bewildered by the enormous amount of material in this book. It should, however, serve as an excellent reference book.

Chronic Rheumatic Diseases. Being the Third Annual Report of the British Committee on Chronic Rheumatic Diseases Appointed by The Royal College of Physicians. Edited by C. W. Buckley, M.D., F.R.C.P., number three. 131 pages. New York: The Macmillan Company, 1937. Cloth $3.50.

The object of these reports is to present an account of the clinical and laboratory observations on the treatment of rheumatic diseases, as gathered from British and other medical centers. Vaccines, physical therapy, and other therapeutic agents are discussed by various authorities. Sympathectomy is emphasized on account of the definite improvement in the general condition of the patient, though no direct improvement is observed in the joints involved. Vaccines are of doubtful value according to one report. X-ray treatment affords subjective improvement in peritendonitis, fibrositis and neuralgias, with a presentation of technic. Emphasis is given the beneficial use of sodium salicylates in gout and other joint diseases. As in all similar reports, the points of view are quite varied, and herein lies its appeal to those interested in such diseases.

The Care and Feeding of Babies in Warm Climates. By Charles James Bloom, B.S., M.D., F.A.C.P., F.A.A.P., Professor of Pediatrics, Graduate School of Medicine, Tulane University of Louisiana; Senior Visiting Pediatrist, Charity Hospital and Touro Infirmary; Co-Chief, Department of Pediatrics, Mercy Hospital; Chief, Department Pediatrics, Flint Goodridge Hospital; Physician-in-Charge, Metairie Park Country Day School, New Orleans; Faculty, Southern Pediatric Seminar, Saluda, North Carolina. 358 pages, illustrated. New Orleans: Pelican Publishing Company, 1937.

This book is intended as a mother's guide and reference book, beginning with pregnancy and the choice of obstetricians and nurses and extending through infancy. The title would lead one to expect more attention than is given to the problems of babies in warm climates. The volume offers an excellent analysis of the modern literature of nutrition as it applies to pediatrics.

Postgraduate Surgery. Edited by Rodney Maingot, F.R.C.S. (Eng.), Senior Surgeon to the Royal Waterloo Hospital and to the Southend General Hospital; Late Chief Assistant to a Surgical Unit, St. Bartholomew's Hospital. Volume III, three volumes, 5,584 pages, illustrated. New York: D. Appleton-Century Company, Inc., 1937. Price, $45.00 for three volumes; sold only in sets.

In the October, 1936, number of the SOUTHERN MEDICAL JOURNAL, Volumes 1 and 2 of Postgraduate Surgery were received. Volume 3 has just been received.

This volume is devoted largely to the surgical specialties, with very interesting chapters on cardiovascular, plastic, obstetrical and orthopedic surgery and to hernia. The author of the chapter on hernia stresses the merits of Gallie's method of repair of herniae with autoplastic fascial sutures. The advantages of Gallie's operations have long been recognized by American surgeons. His condemnation of the Bassini operation seems hardly justified in view of the very favorable results which continue to be achieved in this country.

Other valuable sections are devoted to deep x-ray therapy, venereal disease, syphilis and to surgery of the esophagus and diaphragm.

Volume 3 is fully in keeping with the excellence of the two volumes which preceded it and which have already been reviewed.

Radiation Therapy: Its Use in the Treatment of Benign and Malignant Conditions. By Ira I. Kaplan, B.Sc., M.D., Clinical Professor of Surgery, New York University Medical College; Director, Radiation Therapy Department, Bellevue Hospital, New York. 558 pages, illustrated. New York: Oxford University Press, 1937. Cloth $10.00.

This complete and comprehensive text comprises 536 pages with 198 illustrations. Its 24 chapters cover every condition, benign or malignant, that is usually treated by irradiation. It not only discusses the treatment from the general medical point of view, but gives a very lucid description of the varying technics used in different conditions and sometimes adds a great deal to the picture through his pathologic discussions.

In his chapter on physics of x-ray the author outlines the elementary physical principles of practical significance in radiation therapy and presents it in such a way as to be entirely comprehensible to the average physician and certainly to the physicist and radiologist.

He discusses at length irradiation in the following: skin diseases; ear, nose and throat conditions; breast; gastro-intestinal tract; gynecology; genito-urinary conditions; endocrinology; inflammatory conditions; blood dyscrasias; sarcomas; and bone diseases. The additions of the chapters on complications following irradiation and the nursing care of patients with malignancies are excellent and are of great value to the physician who refers such patients.

Although each section of the book is excellent, the chapter on irradiation of breast conditions is outstanding and worthy of special mention. The author outlines the various breast lesions with a description of their underlying pathology and discusses the treatment of each. The clinical picture of the different types of malignancies and their classification into those which should receive preoperative, postoperative and combined irradiation are of great value.

As a reference, this book can be highly recommended to all radiologists, and the general physician will find it a real addition to his library.

Pocket Atlas of Anatomy. By Victor Pauchet and S. Dupret. Third Edition. 368 pages, illustrated. New York: Oxford University Press, 1937. Cloth $4.00.

Three hundred and forty-five illustrations portray the anatomy of the human body for the student. Each picture is labeled with the nomenclature adopted by the Anatomical Society in Birmingham in 1933: B.N.A. nomenclature is given in brackets when it differs markedly.

There are no legends or text, only the drawings. This makes the work readily available for quick reference.

Southern Medical News

MEDICAL MEETINGS

The Mid-South Postgraduate Medical Assembly will hold its fifty-third annual convention in Memphis at the Peabody Hotel, February 15-18.

The Southeastern Surgical Congress will hold its annual meeting in Louisville at the Brown Hotel, March 7-9.

The second annual New Orleans Graduate Medical Assembly will be held in New Orleans at the Roosevelt Hotel, March 7-10.

The Dallas-Southern Clinical Society will hold its tenth annual spring clinical conference in Dallas at the Hotel Adolphus, March 14-17.

ALABAMA

The Jefferson County Medical Society has elected the following officers: Dr. A. L. Glaze, Birmingham, President; Dr. Lee Turlington, Birmingham. Vice-President; Dr. Robert A. Hamrick, Birmingham, Secretary-Treasurer; and Dr. Lloyd Noland, Birmingham, representative on the Jefferson County Board of Health.

Dr. Julius E. Dunn, Fort Payne, has been appointed Health Officer of Lauderdale County, with headquarters at Florence.

Dr. Samuel D. Sturkie, formerly of Oneonta, has been appointed Health Officer of Chilton County.

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ANNOUNCING THE SECOND ANNUAL

NEW ORLEANS GRADUATE MEDICAL ASSEMBLY

March 7, 8, 9, 10, 1938

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DERMATOLOGY: Dr. Udo J. Wile, Professor of Dermatology and Syphilology, University of Michigan Medical School, Ann Arbor

ENDOCRINOLOGY: Dr. Charles Mazer, Associate Professor of Gynecology, Graduate School of Medicine, University of Pennsylvania

GASTRO-ENTEROLOGY: Dr. Burrill B. Crohn, New York City

GYNECOLOGY: Dr. Norman F. Miller, Professor of Obstetrics and Gynecology, University of Michigan Medical School, Ann Arbor.

MEDICINE: Dr. Richard P. Strong, Professor of Tropical Medicine, Harvard University Medical School, Boston
Dr. Sydney R. Miller, Associate Professor of Medicine, University of Maryland School of Medicine and College of Physicians and Surgeons, Baltimore

NEUROLOGY: Dr. Temple S. Fay, Professor of Neurology and Neurosurgery, Temple University School of Medicine, Philadelphia

OBSTETRICS: Dr. W. C. Danforth, Associate Professor of Obstetrics and Gynecology, Northwestern University Medical School, Chicago

OPHTHALMOLOGY: Dr. Algernon B. Reese, New York City

ORTHOPEDICS: Dr. Philip D. Wilson, Clinical Professor of Orthopedic Surgery, Columbia University College of Physicians and Surgeons, New York City

OTOLARYNGOLOGY: Dr. Frank R. Spencer, Associate Professor of Otolaryngology, University of Colorado School of Medicine, Denver

PATHOLOGY: Dr. Fred W. Stewart, New York City

PEDIATRICS: Dr. A. Graeme Mitchell, Professor of Pediatrics, University of Cincinnati College of Medicine

RADIOLOGY: Dr. Frederick M. Hodges, Professor of Clinical Radiology, Medical College of Virginia, Richmond

SURGERY: Dr. Arthur E. Hertzler, Professor of Surgery, University of Kansas School of Medicine, Halstead

Dr. Harvey B. Stone, Associate Professor of Surgery, Johns Hopkins University, School of Medicine, Baltimore

UROLOGY: Dr. William E. Lower, Cleveland, Ohio

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RESIDENT MEMBERS

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Apply to Assistant Dean, Courses for Graduates, Harvard Medical School, Boston, Massachusetts

Continued from page 232

Dr. John M. Kimmey, Clanton, formerly Health Officer of Chilton County, resigned to accept an appointment as Health Officer of Calhoun County.

Dr. Samuel Logan Stephenson, Jr., and Miss Dorothy D. Compton, both of Fairfield, were married October 30.

Deaths

Dr. Ira Cheleous Ballard, Gadsden, aged 68, died suddenly October 4 of angina pectoris.

Dr. William Franklin Betts, Evergreen, aged 66, died October 29.

Dr. William Everett Quinn, Fort Payne, aged 86, died September 17.

Dr. Jesse McCampbell Reed, Magnolia Springs, aged 47, died September 21.

Dr. Paul Mason Thompson, Bay Minette, aged 32, died October 9 of chronic myelogenous leukemia.

Dr. Felix Marcus Tully Tankersley, Montgomery, aged 39, died September 22, following an operation for appendicitis.

ARKANSAS

The Arkansas Medical Society will hold its next annual meeting in Texarkana, April 18-20.

Bradley County Medical Society has elected the following officers: Dr. M. T. Crow, President; Dr. L. E. Ellison, Vice-President; Dr. W. J. Hunt, Secretary-Treasurer, all of Warren.

Craighead-Poinsett County Medical Society has elected the following officers: Dr. R. H. Willett, Jonesboro, President; Dr. J. W. Elder, Harrisburg, Vice-President; Dr. H. H. McAdams, Jonesboro, Secretary-Treasurer.

The Eighth Councilor District Medical Society has elected the following officers: Dr. Joe Shuffield, Little Rock, President, and Dr. Hoyt Allen, Little Rock, Secretary-Treasurer.

Faulkner County Medical Society has elected the following officers: Dr. W. L. Brittain, President; Dr. G. L. Henderson, Vice-President; and Dr. J. S. Westerfield, Secretary-Treasurer, all of Conway.

Garland County Medical Society has elected the following officers: Dr. Gaston A. Hebert, President; Dr. D. B. Stough, Vice-President; and Dr. W. E. Gray, Secretary-Treasurer, all of Hot Springs National Park.

Jefferson County Medical Society has elected the following officers: Dr. A. W. Troupe, President; Dr. C. J. Higinbotham, Vice-President; Dr. John K. Walker, Secretary-Treasurer, all of Pine Bluff.

Lawrence County Medical Society has elected the following officers: Dr. J. Hughes, Hoxie, President; Dr. W. W. Hatcher, Imboden, Vice-President; and Dr. Chas. L. Tibbels, Black Rock, Secretary-Treasurer.

Lincoln County Medical Society has elected the following officers: Dr. R. L. Johnson, Grady, President; Dr. G. C. Wood, Grady, Vice-President; and Dr. Vernon Tarver, Star City, Secretary-Treasurer.

Mississippi County Medical Society has elected the following officers: Dr. A. E. Robinson, Leachville, President; Dr. J. E. Beasley, Blytheville, Vice-President; and Dr. F. D. Smith, Blytheville, Secretary-Treasurer.

Ouachita County Medical Society has elected the following officers: Dr. E. J. Byrd, Bearden, President; Dr. Sam Thompson, Camden, Vice-President; and Dr. R. B. Robins, Camden, Secretary.

Pulaski County Medical Society has elected the following officers: Dr. R. M. Blakely, President; Dr. S. P. Bond, Vice-President; Dr. E. H. White, Secretary; and Dr. R. J. Calcote, Treasurer, all of Little Rock.

The St. Francis County Medical Society has elected the following officers: Dr. Paul S. Lanier, President; Dr. C. N. Bogart, Vice-President; and Dr. J. O. Rush, Secretary-Treasurer, all of Forrest City.

Sevier County Medical Society has elected the following officers: Dr. C. C. Hanchey, DeQueen, President; Dr. B. E. Hendrix, Gillham, Vice-President; and Dr. G. C. Kimball, Secretary-Treasurer.

Sebastian County Medical Society has elected the following officers: Dr. A. A. Blair, President; Dr. J. W. Amis, Vice-President; Dr. L. M. Henry, Secretary; and Dr. W. R. Brooksher, Treasurer, all of Fort Smith.

Woodruff County Medical Society has elected the following officers: Dr. E. F. Brewer, Augusta, President; Dr. J. W. Morris,

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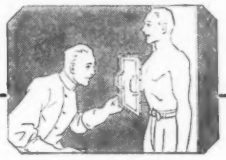

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Continued from page 34

McCrory, Vice-President; and Dr. L. E. Biles, Augusta, Secretary-Treasurer.

The City Hospital Staff of Little Rock has elected as officers: Dr. Joe H. Sanderlin, Chief of Staff; Dr. Randolph T. Smith, Vice-Chief; and Dr. F. Walter Carruthers, Secretary.

Dr. W. F. Shearer, Little Rock, has been elected Vice-President of the Pulaski Heights Lions Club.

Dr. John M. Smith, formerly of Morrilton, is now practicing in Orange, Texas.

Dr. I. R. Johnson and Dr. T. K. Mahan are having constructed a clinic building at Blytheville.

Dr. Frank Vinsonhaler, Little Rock, has been appointed Arkansas Chairman of the Fight Against Infantile Paralysis campaign.

St. Anthony's Hospital at Morrilton elected Dr. H. E. Moblev as Chief of Staff and Dr. E. L. Matthews as Assistant Chief of Staff.

The Tri-State Medical Society, at its meeting in Shreveport, Louisiana, in October, elected Dr. Harry E. Murry, Texarkana, President; Dr. Rufus B. Robins, Camden, one of the Vice-Presidents; and Dr. Ruel R. Robins, Texarkana, Secretary.

DEATHS

Dr. Edward Turner Bramlitt, Malvern, aged 83, died December 18.

Dr. W. A. Clark, Bald Knob, aged 70, died recently.

Dr. John Shepherd Eastland, Judsonia, aged 92, died October 8 of senility.

Dr. Shelby Boone Hinkle, Little Rock, aged 54, died December 5, of a heart attack.

Dr. Robert A. Milliken, Little Rock, aged 46, died November 1.

Dr. J. William Scales, Dexter, aged 73, died December 4.

DISTRICT OF COLUMBIA

The George Washington University will hold its sixth annual Postgraduate Clinic at the University Medical School and Hospital on February 19.

The Jacobi Society of Washington elected the following officers: Dr. Harry A. Spigel, President; Dr. Bernard Notes, Vice-President; Dr. Isadore Levin, Secretary; and Dr. Aaron Nimetz, Treasurer.

Dr. W. A. Applegate, Washington, has retired as Chief Surgeon of the Southern Railway System, after having served thirty-two years.

Dr. John Francis McGuire, Jr., Washington, and Miss Rita May Connors, of Miami, Florida, were married September 18.

DEATHS

Dr. Anthony A. Deep, Washington, aged 39, died suddenly December 12.

Dr. William C. Fowler, Washington, aged 73, died November 19, following an operation.

Dr. Raymond Thomas Holden, Washington, aged 77, died October 16, of coronary thrombosis.

Dr. William E. Whitson, Washington, aged 63, died December 3.

FLORIDA

Duval County Medical Society has elected the following officers: Dr. J. Lunsford Boone, President; Dr. Thomas E. Buckman, President-Elect; Dr. B. F. Woolsey, Vice-President; Dr George W. Croft, Secretary; and Dr. Alan D. Brown, Treasurer, all of Jacksonville.

Lake County Medical Society has elected the following officers: Dr. H. T. Fenn, Mount Dora, President; Dr. W. G. DeVane, Groveland, Vice-President; and Dr. W. L. Ashton, Umatilla, Secretary-Treasurer.

Leon-Gadsden-Liberty-Wakulla-Jefferson County Medical Society has elected the following officers: Dr. W. D. Rogers, Chattahoochee, President; Dr. S. E. Wilhoit, Quincy, Vice-President; and Dr. B. A. Wilkinson, Tallahassee, Secretary-Treasurer.

The Nurses' Home at the Florida State Hospital at Chattahoochee, now under construction, is expected to be completed in the spring. This new building, which will cost $228,946.00, replaces the structure destroyed by fire last winter.

Dr. and Mrs. S. B. Forbes, Tampa, have returned from

Continued on page 38

THE NEW YORK POLYCLINIC
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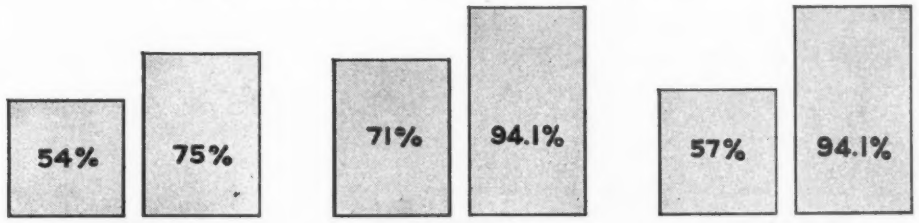

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Continued from page 36

Europe. Dr. Forbes has been doing postgraduate work in Vienna.

Dr. and Mrs. E. J. Melville, St. Petersburg, have returned after spending some time in the Orient and Australia.

Dr. Ralph Green, Coral Gables, now Medical Director of Eastern Air Lines and Medical Consultant for Pan American Airways, has been appointed by the Aero-Medical Association of the United States Chairman of a special committee for the purpose of instituting a pilot fatigue study, this at the request of the Bureau of Air Commerce.

Dr. Herbert L. Bryans, Pensacola, has been elected President of the Gulf Coast Clinical Society.

Dr. N. McLane, Pensacola, spent a month in St. Louis, Missouri, attending clinics at Barnes Hospital.

Dr. J. O. W. Rash, Miami, has returned from a three weeks' vacation in Europe.

Dr. William C. Roberts recently completed the construction of the William Carmel Roberts Clinic at Panama City. At the official opening the clinic was dedicated to the owner's father, Dr. W. P. Roberts, of Dothan, Alabama.

Dr. William H. Kupper, who has been in charge of malaria therapy at the State Hospital, work sponsored by the Rockefeller Foundation in collaboration with the State Board of Health, has resigned from the staff to practice in Hollywood.

Dr. H. Hamilton Cooke, Miami, was elected Vice-President in the Section on Neurosurgery of the Pan American Medical Association.

Dr. Paul G. Shell, formerly Director of Broward County Health Unit, has opened offices at Tampa.

Dr. Duncan T. McEwan and Dr. C. D. Hoffman, both of Orlando, were elected to Fellowship at the recent meeting of the American College of Surgeons, held in Chicago.

Dr. J. W. McMurray, formerly Director of the Gulf-Calhoun-Franklin Unit, was recently appointed Director of the Broward County Health Unit with headquarters at Ft. Lauderdale.

Dr. and Mrs. A. R. Beyer, Tampa, have returned from abroad. Dr. Beyer spent several months doing postgraduate work in Vienna.

Dr. Thomas E. Morgan, Health Officer of Pinellas County with headquarters in Clearwater, has been appointed regional medical consultant to the Children's Bureau of the U. S. Department of Labor for the southeastern district. He will now have his headquarters in Washington, D. C.

Dr. Noble A. Upchurch, City Health Officer of Jacksonville, was elected President of the Florida Public Health Association, succeeding Dr. Wilbur A. McPhaul.

Dr. Hugh West, Deland, and Miss Elizabeth Ann Rhett, of Davidson, North Carolina, were married October 9.

Deaths

Dr. Robert Bunyan Ayer, Gainesville, aged 71, died October 29, of injuries received in an automobile accident.

Dr. Wellington B. Coffeen, Miami, aged 78, died October 17, of injuries received in a fall.

Dr. Grover C. Hardie, Ft. Pierce, died October 25, of coronary thrombosis.

Dr. Alexander M. Steen, Palatka, aged 76, died October 8, of cerebral embolism.

Dr. Leslie Washington Weedon, Tampa, aged 77, died November 12, of dilatation of the heart.

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GEORGIA

The Medical Association of Georgia will hold its eighty-ninth annual session in Augusta at the Forest Hills Hotel, April 26-29.

The Atlanta Graduate Medical Assembly was held in Atlanta, January 25-28.

The Southern Section of the American Laryngological, Rhinological and Otological Society, Incorporated, was held in Atlanta, January 24.

Dr. J. W. Palmer, Ailey, was reelected Secretary of the Association of Seaboard Air Line Railway Surgeons at their meeting, held in November in Miami, Florida.

Dr. J. R. Garner, Atlanta, Chief Surgeon for the Atlanta and West Point Railroad Company, the Western Railway of Alabama, and the Georgia Railroad, was appointed to represent the Association of American Railroads at the meeting of the Air Hygiene Foundation, Incorporated, held in Pittsburgh on November 30–December 2.

Dr. J. C. Verner has been appointed local surgeon for the Southern Railway System at Commerce.

Dr. Champneys H. Holmes, Atlanta, President-Elect of the American College of Chest Physicians, has been asked to serve as a member of the Committee on Nominations of Directors by the National Tuberculosis Association. Only five members are appointed and Dr. Holmes represents the Southern states.

Dr. Howard Hailey and Dr. Hugh Hailey announce their association in the practice of dermatology and syphilology with offices in the Candler Building, Atlanta.

Dr. Roger C. Swint, Atlanta, has been named Superintendent Emeritus by the State Board of Public Welfare, the title being awarded to him for his thirty-two years of service to the mentally sick of Georgia.

Dr. Isham W. Irvin, Albany, was presented a silver service by the Dawson Kiwanis Club as a token of appreciation for his work in behalf of unfortunate children in Dawson and Terrell County.

Dr. Edgar Walter Stephens, Jr., Atlanta, and Miss Ida Lee Mattison, Augusta, were married October 15.

Deaths

Dr. Abner Wellborn Calhoun, Atlanta, aged 40, died November 3.

Dr. Rufus Thomas Dorsey, Atlanta, aged 64, died November 9, of heart disease.

Dr. Lewis Sage Hardin, Atlanta, aged 64, died November 12.

KENTUCKY

The annual meeting of the Kentucky State Medical Association will be held in Louisville in the early fall with headquarters at the Brown Hotel.

Carlisle County Medical Society has elected the following officers: Dr. J. F. Dunn, Arlington, President; Dr. G. W. Payne, Bardwell, Vice-President; and Dr. E. E. Smith, Bardwell, Secretary.

Harrison County Medical Society has elected the following officers: Dr. K. W. Brumback, Cynthiana, President; Dr. C. L. Swinford, Cynthiana, Vice-President; and Dr. W. B. Moore, Cynthiana, Secretary-Treasurer.

Jefferson County Medical Society has elected the following officers: Dr. J. Duffy Hancock, President; Dr. Oscar O. Miller,

Continued on page 40

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(See back of this page)

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"*The clinical value of encephalography, well performed and correctly interpreted, cannot be overestimated. The procedure has made possible many a correct diagnosis and prevented numerous useless cranial operations.*"—RADIOLOGY, *24*:85, Jan., 1935

"*In skull examinations, by adapting the technic [radiographic], a fracture may be demonstrated, the existence of which would otherwise not be suspected.*"—RADIOLOGY, *18*:320, Feb., 1932

The obvious excellence of the original radiograph from which the reproduction printed on the reverse side of this page was made is due, first, to the knowledge of the radiologist; second, to the use of Eastman X-ray Film.

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Continued from page 38

President-Elect; Dr. Karl D. Winter, First Vice-President; Dr. Lee Palmer, Second Vice-President; Dr. Archer T. Hurst, Secretary; and Dr. John T. Bate, Treasurer, all of Louisville.

Whitley County Medical Society has elected the following officers: Dr. L. L. Terrell, Corbin, President; Dr. F. S. Smith, Corbin, Vice-President; and Dr. C. A. Moss Williamsburg, Secretary and Treasurer.

Dr. Maurice G. Buckles announces the practice of diseases of the lungs, bronchoscopy and pneumothorax with offices in the Heyburn Building, Louisville.

Dr. Edward M. Thompson, Munfordville, formerly Health Officer of Hart County, is now Health Officer of Logan County.

Deaths

Dr. Henry C. Clark, Falmouth, aged 89, died October 31, of pneumonia.

Dr. Charles Alsop DeWitt, Jr., Louisville, aged 32, died September 24, of pneumonia.

Dr. George W. Ragan, Cold Spring, aged 72, died September 27, of heart disease.

Dr. Lewis Ryans, Louisville, aged 66, died September 26, of arteriosclerosis and endocarditis.

Dr. Joel Buford Scholl, Jabez, aged 70, died September 4.

LOUISIANA

Avoyelles Parish Medical Society has elected the following officers: Dr. A. B. Cairns, Bunkie, President; Dr. L. W. Holloman, Marksville, Vice-President; and Dr. Kirby A. Roy, Mansura, Secretary-Treasurer.

Bi-Parish Medical Society has elected the following officers: Dr. C. S. Toler, Clinton, President; Dr. W. J. Roberts, Felixville, Vice-President; and Dr. E. M. Toler, Clinton, Secretary-Treasurer.

Red River Parish Medical Society has elected the following officers: Dr. W. L. Davis, Coushatta, President; Dr. L. S. Huckabay, Harmon, Vice-President; and Dr. W. W. Gahagan, Coushatta, Secretary-Treasurer.

St. Tammany Parish Medical Society has elected the following officers: Dr. Frank F. Young, Covington, President; Dr. F. R. Singleton, Slidell, Vice-President; and Dr. H. D. Bulloch, Covington, Secretary-Treasurer.

Tri-Parish Medical Society has elected the following officers: Dr. E. O. Edgerton, Tallulah, President; Dr. Joseph Whitaker, St. Joseph, Dr. Fritz A. LaCour, Oak Grove, and Dr. B. C. Abernathy, Sondheimer, Vice-Presidents; and Dr. Dean H. Allen, Tallulah, Secretary-Treasurer.

Washington Parish Medical Society has elected the following officers: Dr. Norton Voorhies, Bogalusa, President; Dr. Rawlin R. Ward, Bogalusa, Vice-President; and Dr. Benjamin Freedman, Franklinton, Secretary-Treasurer.

The library of Tulane University of Louisiana School of Medicine, New Orleans, has been named the Rudolph Matas Medical Library in honor of Dr. Rudolph Matas, Emeritus Professor of Surgery at the University.

The Highland Sanitarium, Shreveport, elected the following officers: Dr. J. V. Hendrick, President; Dr. T. B. Tooke, Vice-President; and Dr. Albert Owers, Secretary-Treasurer.

Dr. Dean H. Echols, formerly instructor in neurological surgery ot the University of Michigan Medical School, announces the practice of neurological surgery with offices in the American Bank Building in New Orleans.

Dr. Harry Vernon Sims, New Orleans, was elected President of the Southern Interurban Gynecological and Obstetrical Society at its seventh annual meeting in New Orleans, November 30.

Dr. Charles A. Bahn, New Orleans, has been reelected President of the Louisiana Society for the Prevention of Blindness.

Dr. A. F. Brock, New Orleans, has been appointed Assistant coroner for Orleans Parish, succeeding Dr. E. B. Gill, who resigned.

The Alumni Association of the Eye, Ear, Nose and Throat Hospital has chosen Dr. Lucian W. Alexander, President; Dr. Kotz Allen, Vice-President; and Dr. Philip J. Bayon, Secretary-Treasurer. Drs. Francis LeJeune and M. P. Boebinger were elected among the councilors. All of these physicians are of New Orleans.

Continued on page 42

FOR the failing heart of middle life give Theocalcin, 2 or 3 tablets, t.i.d., with meals, to aid in reducing edema, diminishing dyspnoea, and in strengthening heart action. After relief is obtained, the comfort of the patient can often be continued with smaller doses.

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**Jr. A.M.A.—March 13, 1937. Vol. 108, p. 853.*

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Continued from page 40

Dr. R. L. Gordon was elected President of the New Orleans Urological Society at their recent annual meeting.

Dr. James C. Cole, New Orleans, was elected President of the Aero Medical Society of the United States at a meeting held in New York City.

Assistant Surgeon Paul T. Erickson was relieved from duty at the U. S. Quarantine Station, New Orleans, recently and ordered to Seattle, Washington, to report for duty.

Assistant Surgeon Harris Isbell, formerly on duty at the U. S. Quarantine Station, Angel Island, California, was ordered to New Orleans to report to the Medical Officer in Charge, U. S. Marine Hospital, for duty.

Surgeon Harry E. Trimble was relieved from duty at the U. S. Quarantine Station, New Orleans, recently and ordered to Galveston, Texas, to assume charge of U. S. Marine Hospital there.

Dr. Sidney J. Rozas, Opelousas, has been elected Chairman of the St. Landry division of the Louisiana Society for Crippled Children.

Death

Dr. John Sherwood McBride, Ansley, aged 77, died September 13.

MARYLAND

A building program for mental institutions in Maryland, representing an expenditure of $1,124,000, was recently launched by the state. The program includes a new dormitory and kitchen at the Rosewood Training School to cost $350,000; a new building for tuberculous patients and a home for male employees at Springfield State Hospital; a new dormitory for patients at Eastern Shore State Hospital; and a new dining room at Spring Grove State Hospital.

Dr. E. Eugene Covington, Baltimore, practice limited to general surgery and radium therapy, was given the certificate on Radiation Therapy issued by the American Medical Association Board of Radiology at their Atlantic City meeting last year.

Dr. Eugene C. Peck, Oakland, formerly Health Officer of Garrett County, has been appointed Health Officer of St. Mary's County.

Deaths

Dr. Harry Adler, Baltimore, aged 65, died November 1, of heart disease.

Dr. John H. Drach, Cockeysville, aged 77, died September 11.

Dr. Joseph Wm. Long, Walkersville, aged 58, died December 14, of coronary thrombosis.

MISSISSIPPI

Clarksdale and Six Counties Medical Society has elected the following officers: Dr. J. D. House, Sledge, President; Dr. H. L. Cockerham, Vice-President, Bolivar County; Dr. Wm. P. Warfield, Vice-President, Coahoma County; Dr. J. P. Walker, Vice-President, Quitman County; Dr. John A. Harris, Vice-President, Tallahatchie County; Dr. W. H. Williams, Vice-President, Tunica County; and Dr. N. C. Knight, Clarksdale, Secretary-Treasurer.

The Coast Counties Medical Society was recently formed by the amalgamation of the Harrison-Stone-Hancock Counties Medical Society and the Jackson County Medical Society, bringing all the counties in the ninth district into one organization. Dr. Edwin B. Van Ness, Gulfport, is President, and Dr. Daniel L. Hollis, Biloxi, Secretary.

At the regular staff meeting of the Greenwood LeFlore Hospital, Greenwood, Dr. W. E. Denman was elected Chief-of-Staff, Dr. J. A. Crawford, Vice-President, and Dr. I. B. Bright, Secretary-Treasurer.

Dr. Felix J. Underwood, Jackson, has been appointed a member of the Rockefeller Foundation Board to serve for a period of three years. This Board is composed of six members and decides the policy of the Foundation throughout the world.

Dr. Johnny Rufus Johnson has reopened his office in the Standard Life Building, Jackson, practice limited to urology and proctology.

Deaths

Dr. James M. Barnett, Okolona, aged 62, died in October.

Dr. Samuel R. Deanes, West Point, aged 75, died recently.

Dr. William Meade Eggleston, Vicksburg, aged 81, died September 19, of malignancy of the pancreas.

Dr. James Elvis Luter, Clarksdale, aged 71, died October 6, of heart disease.

Dr. Robert L. Mercer, Shelby, aged 69, died September 10.

Dr. N. W. Nanney, Fulton, aged 57, died recently.

Continued on page 44

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Richmond, Virginia

Continued from page 42

Dr. Claudius W. Stewart, Osyka, aged 59, died October 13, of injuries received in an automobile accident.

MISSOURI

Boone County Medical Society has elected the following officers: Dr. Dan G. Stine, Columbia, President; Dr. E. D. Baskett, Columbia, Vice-President; and Dr. M. E. Cooper, Secretary-Treasurer, reelected.

Buchanan County Medical Society has elected the following officers: Dr. G. T. Bloomer, President; Dr. F. X. Hartigan, Vice-President; Dr. O. Earl Whitsell, Secretary; and Dr. J. M. Bell, Treasurer, all of St. Joseph.

Butler County Medical Society has elected the following officers: Dr. B. J. McCauley, Poplar Bluff, President; Dr. C. Lilbourn Qualls, Poplar Bluff, Vice-President; and Dr. J. Lester Harwell, Poplar Bluff, Secretary-Treasurer.

Cass County Medical Society has elected the following officers: Dr. L. V. Murray, Pleasant Hill, President; Dr. G. W. Griffith, Garden City, Vice-President; and Dr. D. S. Long, Harrisonville, Secretary-Treasurer.

Chariton County Medical Society has elected the following officers: Dr. U. G. Buck, Rothville, President; Dr. O. H. Damron, Keytesville, Vice-President; and Dr. G. W. Hawkins, Salisbury, Secretary and Treasurer.

Grundy-Daviess County Medical Society has elected the following officers: Dr. W. A. Fuson, Trenton, President; Dr. O. R. Rooks, Trenton, Vice-President; and Dr. E. A. Duffy, Trenton, Secretary and Treasurer.

Jackson County Medical Society has elected the following officers: Dr. Ferdinand C. Helwig, President-Elect; Dr. James Harvey Jennett, Secretary; and Dr. Ambrose Eastin Eubank, Treasurer, reelected, all of Kansas City.

Nodaway County Medical Society has elected the following officers: Dr. W. R. Jackson, Maryville, President; Dr. C. V. Martin, Maryville, Vice-President; and Dr. B. F. Byland, Burlington Junction, Secretary-Treasurer.

Pettis County Medical Society has elected the following officers: Dr. Gordon Stauffacher, President; Dr. E. H. Schaefer, Vice-President; Dr. A. E. Monroe, Treasurer; and Dr. John B. Carlisle, Secretary, all of Sedalia.

Saline County Medical Society has elected the following officers: Dr. E. A. Belden, Marshall, President; Dr. S. T. Mead, Slater, Vice-President; Dr. John R. Lawrence, Marshall, Secretary and Treasurer.

St. Louis County Medical Society has elected the following officers: Dr. Roy Walther, Overland, President; Dr. D. M. Skilling, Jr., Webster Grove, Vice-President; and Dr. John A. Rogers, University City, Secretary.

Ste. Genevieve County Medical Society has elected the following officers: Dr. J. A. Wilkens, St. Mary's, President, reelected; Dr. G. M. Rutledge, Ste. Genevieve, Vice-President; and Dr. R. W. Lanning, Ste. Genevieve, Secretary-Treasurer, reelected.

American Public Health Association will hold its sixty-seventh annual meeting in Kansas City, October 25-28. Affiliated organizations meeting with this Association are the American Association of School Physicians, Association of Women in Public Health, Conference of State Laboratory Directors, Conference of State Sanitary Engineers, American Association of State Registration Executives, Delta Omega and the International Society of Medical Health Officers. Dr. Edwin H. Schorer, Director, Kansas City Health Department, is Chairman of the local committee.

The second annual Clinical Conference of the Midwestern Radiologists will be held in Kansas City at the Muehlebach Hotel, February 11 and 12. Dr. Ira H. Lockwood, Kansas City, is Chairman of the local committee.

Deaths

Dr. Isaac W. Amerman, Nevada, aged 86, died October 29, of coronary thrombosis.

Dr. Ulysses S. Grant Arnold, Martinsburg, aged 72, died September 19, of adenomatous goiter.

Dr. Alvah Clayton Bridges, Kahoka, aged 67, died September 5, of cardio-vascular degeneration.

Dr. William Mead Sams, Kansas City, aged 71, died in September of coronary thrombosis.

Dr. Cullen O. Thomas, Worthington, aged 60, died September 9.

Dr. Harry W. Tull, Carrollton, aged 69, died October 1, of cerebral hemorrhage.

Dr. George Williams, Independence, aged 78, died October 16, of cerebral hemorrhage.

NORTH CAROLINA

Robeson County Medical Society has selected the following officers: Dr. John Knox, Lumberton, President; Dr. S. McIntire, Lumberton, Vice-President; and Dr. L. R. Hedgpeth, Lumberton, Secretary.

The North Carolina Society of Ophthalmology and Otolaryngology at its meeting held in Charlotte, elected Dr. Casper W. Jennings, Greensboro, President; Dr. Frank Smith, Charlotte, Vice-President; and Dr. M. R. Gibson, Raleigh, Secretary-Treasurer.

High Point Board of Health has named Dr. I. T. Mann, Chairman, Dr. Philip B. Davis, Secretary, and other members of the Board are Drs. A. A. York, W. T. Tice and A. C. Jones, all of High Point.

The University of North Carolina School of Medicine, Chapel Hill, received $1,000.00 from Mrs. Charles E. Kistler, Morganton, to be used toward the establishment of a Charles E. Kistler memorial library in the medical sciences. This gift was made in honor of the late Mr. Kistler, a graduate of the University, who had a special interest in the medical school. Mrs. Kistler plans to make an annual gift of this amount.

A new state sanatorium for tuberculosis, built at a cost of $625,000 at Black Mountain, near Asheville, was dedicated November 11. Dr. Paul P. McCain is Superintendent and Dr. Samuel M. Bittinger is Medical Director and Associate Superintendent.

The H. F. Long Hospital, Statesville, will have the capacity of the hospital increased to seventy beds by the addition of a new two-story structure.

The Wake Forest College School of Medicine, Wake Forest, in cooperation with Rex Hospital, Raleigh, plans to establish a school of Medical Technology, and Dr. Coy C. Carpenter, Dean of the Wake Forest Medical School, will be director of the school.

Dr. Felda Hightower, formerly assistant surgeon at the Anson

Continued on page 46

To Assure Quick Dependable Response
Discriminating Physicians are Prescribing
the easily soluble
ACCEPTED AMERICAN MEDICAL ASSN.
DUBIN AMINOPHYLLIN
THEOPHYLLINE-ETHYLENEDIAMINE
American Made from American Materials
H.E.DUBIN LABORATORIES
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Fulfills the Objective of Therapeusis in

Spastic Colitis

The inconsistent results from the usual symptomatic therapy in this condition have long "plagued" the clinician. This is due to the difficulty of correlating therapy with the alternating symptoms of constipation and diarrhea.

The object of treatment is to prevent segmented fragmentation of stools during the diarrheal stage and avoid hard, dehydrated fecal masses during the period of constipation.

These much desired objectives can be accomplished by the use of

MUCILOSE GRANULES or MUCILOSE FLAKES

Mucilose offers a hemicellulose (vegetable gum) prepared by a special process from the Plantago loeflingii. It helps correct some of the harmful factors in colitis and constipation by holding water in the feces, maintaining the *normal fecal colloid,* increasing responsiveness to peristalsis and acting naturally to secure normal bowel rhythm.

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Detroit, Michigan
Please send me a supply of Mucilose for clinical test.

Dr.....

Address.....

City.....State.....

Continued from page 44

Sanitorium, Wadesboro, has been appointed surgeon to the Raleigh Central Prison, succeeding Dr. George S. Coleman.

Dr. Jefferson Davis, Statesville, has been commissioned in the Medical Corps of the United States Navy and transferred to Spartanburg.

Dr. L. B. Skeen, formerly of Troy, has been appointed physician to the State Sanatorium for the Tuberculous Sanatorium, succeeding Dr. R. T. Jenkins.

Dr. Robert A. Ross, Durham, was reelected Secretary of the Southern Interurban Gynecological and Obstetrical Society at its last annual meeting in New Orleans, Louisiana.

Dr. James Daniel Royster, Elm City, and Miss Virginia Dean, of Halifax, Virginia, were married August 16.

Dr. O. Norris Smith, Durham, and Miss Rebecca Hines, Winston-Salem, were married November 10.

Dr. Frank Elmore Wilson, Mooresville, and Miss Esther Colman Hambley, Salisbury, were married in November.

DEATHS

Dr. Thomas C. Blackburn, Hickory, aged 68, died recently.

Dr. Mark Russell Braswell, Rocky Mount, aged 73, died November 15, following a cerebral hemorrhage.

Dr. C. L. Buchanan, Union Mills, aged 63, died November 19, after a year's illness.

Dr. D. A. Burres, High Point, aged 57, died December 2.

Dr. Clyde E. Cotton, Asheville, aged 75, died November 29, of myocardial failure.

Dr. Ronda Horton Hardin, Banners Elk, aged 44, died October 9, of coronary thrombosis and ruptured gastric ulcer.

Dr. Henry Hill Harrison, Asheville, aged 54, died November 20, of coronary thrombosis.

Dr. Percy Wingate Olive, Fayetteville, aged 58, died October 12, of acute dilatation of the heart.

Dr. G. H. Sumrell, Ayden, aged 43, died November 22, following a heart attack.

OKLAHOMA

Dr. O. L. Parsons, Lawton, has been appointed Health Superintendent of Comanche County to succeed Dr. L. C. Knee of Lawton.

Dr. H. K. Speed, Jr., Sayre, has been named Medical Superintendent of the new Western Oklahoma Charity Hospital at Clinton.

Dr. Giles E. Harris, Hugh, has been appointed Health Superintendent of Choctaw County to succeed Dr. Walter N. John, Hugo.

Dr. Forrest S. Etter, Bartlesville, has been appointed Health Superintendent of Washington County.

DEATHS

Dr. Ernest Lee Cox, Jacksonville, aged 72, died September 17, of chronic myocarditis.

Dr. Isaac N. Cottle, Oklahoma City, aged 59, died October 9, of acute dilatation of the heart.

Dr. Gwen Whelpley Crawford, Bartlesville, aged 30, died November 23, of a broken neck received in an automobile collision.

Dr. A. B. Davis, Wilson, aged 45, died January 12.

SOUTH CAROLINA

The Columbia Medical Society has elected the following officers: Dr. R. B. Durham, President; Dr. W. F. Beckham, Vice-President; Dr. J. M. Davis, Secretary; and Dr. T. D. Dotterer, Treasurer, all of Columbia.

The Tri-State Hospital Association, including the Hospital Associations of Virginia, North and South Carolina, will be held at Columbia, April 14-16.

Dr. John F. Busch, Greenville, has resigned as Superintendent of the Greenville County Sanatorium, and joined the staff of the Georgia State Board of Health.

Dr. Andrew A. Walden, North Augusta, was chosen as the outstanding citizen of the town by the local post of the American Legion.

Dr. Wilbur Curtiss Hunsucker is now associated with Dr. Douglas Jennings, Bennettsville, in the practice of surgery, gynecology and obstetrics.

Dr. Allen J. Johnston, formerly chief resident physician at the Columbia Hospital, is now associated with Dr. James L. Martin at Mullins in the practice of medicine.

Dr. O. D. Busby has been elected Mayor of Springfield.

Dr. and Mrs. S. M. Pitts, Saluda, celebrated their Golden Wedding Anniversary on December 8.

Continued on page 48

BUFFERED ALKALINIZATION

by the safe, physiological process

WHERE buffered alkalinization is desirable—as during sulfanilamide administration, in the treatment of colds, influenza and other seasonal respiratory affections—Kalak offers these clinical advantages:

(1) It presents a balanced combination of bicarbonates in solution. (2) It contains the mineral substances normal to the blood (and no other).

Kalak's high buffering value helps to maintain the urinary pH of 7.4 which has been found so desirable in sulfanilamide therapy.

KALAK

is synthetically prepared—is hypertonic, uniform in composition, definite in alkali potency.

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HEMATINIC PLASTULES

Recovery from hypochromic anemia, in cases treated with Hematinic Plastules, is usually rapid and unrestrained as evidenced by the early increase in the hemoglobin of the red blood cells. The suggested daily dose of only three Hematinic Plastules Plain replaces massive iron feedings and diminishes the likelihood of gastric disturbances, constipation and diarrhea . . . . Hematinic Plastules provide ferrous iron and vitamins B and G in soluble gelatin capsules, available in two types, Plain and with Liver Extract. Inquiries from physicians are given prompt attention.

THE BOVININE COMPANY • CHICAGO, ILLINOIS

Continued from page 46

DEATHS

Dr. Francis Marion Griffin, Lynchburg, aged 51, died October 2, of diabetes mellitus and gangrene.

Classified Advertisements

WANTED—Thoroughly trained men in orthopedics and eye, ear, nose and throat, preferably men recently graduated from A-1 school and just finishing residences, to become associated with clinic in South Florida. Address C. E. T., care JOURNAL.

POSITION DESIRED—Fully qualified physician desires permanent hospital staff appointment or group clinic appointment with practice limited to anesthesia. Address inquiries to Dept. 9, care Southern Medical Association, Birmingham, Alabama.

RESIDENT INTERN in seventy-bed Tuberculosis Sanitarium in mid-Southern city. Send reference age,, college and hospital experience. Salary $100.00 per month and maintenance. Write F.C.S., care SOUTHERN MEDICAL JOURNAL, Birmingham, Alabama.

ANXIOUS to get in touch with a good eye, ear, nose and throat man. Splendid location in the heart of the Tennessee Valley Project. Must be of good personality and well qualified professionally. There is nothing to sell. Please address your inquiries Dept. 65N, care of this JOURNAL.

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Thousands of babies have been raised upon HORLICK'S — the Original Malted Milk. It is an easily digested, dependable diet, often acceptable when other foods fail. HORLICK'S is a valuable and nourishing food-drink for nursing mothers.

Samples Gladly Sent on Request

HORLICK'S MALTED MILK CORP.
RACINE, WIS.

TENNESSEE

Dyer, Lake and Crockett Counties Medical Society has elected the following officers: Dr. J. O. McKinney, Friendship, President; Dr. J. E. Frazier, Newbern, Vice-President, Dyer County; Dr. J. P. Moon, Tiptonville, Vice-President, Lake County; Dr. W. H. Stallings, Friendship, Vice-President, Crockett County; and Dr. C. L. Denton, Dyersburg, Secretary.

The Five-County Medical Society (Hardin, Lawrence, Lewis, Perry, and Wayne Counties), has elected the following officers: Dr. J. T. Keeton, Clifton, President; Vice-Presidents: Dr. Henry N. Moore, Savannah, Hardin County; Dr. Leo Harris, Lawrenceburg, Lawrence County; Dr. Paul Wiley, Hohenwald, Lewis County; Dr. W. E. Turner, Lobelville, Perry County; Dr. D. L. Woods, Waynesboro, Wayne County. Dr. O. H. Williams, Savannah, was reelected Secretary.

Memphis and Shelby County Medical Society has elected the following officers: Dr. J. H. Francis, President; Dr. W. C. Colbert, Vice-President; Dr. E. G. Kelly, Treasurer; and Dr. A. F. Cooper, Secretary, reelected, all of Memphis.

Dr. Philip Lewis Lyle and Miss Patsy Geraldine Rudolph, both of Clarksville, were married November 20.

DEATHS

Dr. Joseph K. Baker, Mooresburg, aged 68, died September 20.

Dr. Samuel McChesney Ryburn, Morristown, aged 60, died September 22.

Dr. J. Sam Taylor, Clinton, aged 60, died November 24.

Dr. Clarence Baker Agnew Turner, Dyersburg, aged 56, died October 2, of cardiovascular renal disease.

TEXAS

The State Medical Association of Texas will hold its next annual meeting in Galveston, May 9-12.

The Texas Public Health Association, at its fifteenth annual meeting held in Dallas in November, elected the following officers: Dr. Ben M. Primer, Amarillo, President; Dr. A. E. Hill, Tyler, Miss Frances Gale, R.N., San Antonio, Dr. Walter Kleberg, Galveston, and Dr. M. B. Starnes, Dallas, Vice-Presidents; Mr. P. A. Kerby, Austin, Secretary-Treasurer. The next meeting will be held in San Antonio, November 7-9.

Clay-Montague-Wise Counties Society has elected the following officers: Dr. E. W. Wright, Bowie, President; Dr. F. M. Patton, Bluegrove, Vice-President; and Dr. S. J. Petty, Decatur, Secretary-Treasurer.

The new $3,000,000 Fort Sam Houston Station Hospital was dedicated in December.

The Jacksboro Clinic Hospital, Jacksboro, established and owned by Drs. C. C. McClure and Paul K. Conner, held its formal opening recently.

Wichita Falls State Hospital, Wichita Falls, has been enlarged by a new psychopathic ward, constructed at a cost of $227,000.

A twenty-bed hospital for Hutchinson County was opened at Borger in October, many of the rooms being furnished by firms, individuals and clubs of Borger. The site was donated by John F. Weatherly, Panhandle, and the building cost $65,000.

Dr. Dwight R. Knapp recently leased the Secor Hospital, at Kerrville, from Dr. J. D. Jackson and he purchased the equipment from Mrs. Secor, wife of the late Dr. William L. Secor. The institution will be available to any member of the county medical society.

St. Joseph's Hospital, El Paso, has appointed to its regular staff Drs. R. B. Homan, Sr., Ralph Homan, and R. B. Homan, Jr.

Dr. Frank Goodwin, El Paso, has opened an x-ray and physiotherapy department in his offices.

Dr. J. M. Estes, Jr., Abilene, has been appointed physician for Hardin Simmons University, succeeding his father, the late Dr. J. M. Estes.

Dr. C. D. Strother, Sherman, has been appointed City Health Officer.

Dr. Y. F. Hopkins, Taylor, has been doing postgraduate work at the Mayo Clinic, Rochester, Minnesota.

Dr. Ben N. Ard has moved from Sulphur Springs to Anton.

Dr. Theodore H. Armstrong has moved from Needville to Carlsbad, New Mexico.

Dr. Charles H. Bishop has moved from Wichita Falls to Detroit, Michigan.

Continued on page 50

IN AMENORRHEA and ASSOCIATED DISORDERS

Estrogen Therapy with Progynon-DH and Progynon-B

FUNCTIONAL amenorrheas are usually due to a sub-threshold effect of follicular sex hormone on the uterus. The endometrium fails to reach that stage of development essential to normal menstruation.

Amenorrheic patients complain of a host of symptoms which may be relieved by establishing the menstrual flow and rhythmicity of function. The importance of amenorrhea is recognized, furthermore, in connection with associated disorders, such as infantilism and accompanying dysmenorrhea, and certain cases of sterility.

Authoritative published reports show encouraging results with estrogen therapy with Progynon-DH* Tablets and Progynon-B* Ampules.

These materials have also been successfully used in menopausal disorders, infantile gonorrheal vaginitis, nausea and vomiting of pregnancy.

Progynon-DH Tablets are available in 50, 200 and 600 Active Biological Unit strengths; Progynon-DH Vaginal Suppositories, in 250 Rat Unit (juvenile and adult sizes) and 2500 Rat Unit (adult size) strengths; Progynon-B, in a solution of oil. in ampules of 500, 1000, 2000 and 10,000 Rat Units.

FOR ADDITIONAL INFORMATION PLEASE ADDRESS
THE MEDICAL RESEARCH DIVISION

SCHERING

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BLOOMFIELD NEW JERSEY

Continued from page 48

Dr. Thelma E. Frank has moved from Freer to Benevides.

Dr. Joaquin Gonzales has moved from San Antonio to Laredo.

Dr. Prentiss L. Hyder has moved from Denton to Corpus Christi.

Dr. Roy W. Key has moved from Sherman to Spokane, Washington.

Dr. D. O. Long has moved from Houston to Kerrville.

Dr. Paul C. Pedigo has moved from McCamey to Strawn.

Dr. T. A. Searcy has moved from Lagrange to Hearne.

Dr. H. J. Strieder has moved from Rowena to Shiner.

Dr. V. D. Thomas has moved from Terrell to Whitfield, Mississippi.

Dr. Spencer T. Trice, Halco, and Miss Hazel Dell Graham, Texarkana, were married November 13.

Dr. Leon F. Hutchins, San Angelo, and Miss Nan Mabel Lord, Nashville, Tennessee, were married in November.

Dr. Glenn DeVere Carlson, Dallas, and Miss Lorraine Frances Manske, Sagerton, were married December 6.

Dr. Eugene Flynn, Corpus Christi, and Miss Birdie Kenny, of Galway, Ireland, were married July 3.

Deaths

Dr. Silas James Alexander, Hearne, aged 55, died October 31, of cirrhosis of the liver.

Dr. Herman Isaac Edward Blackman, Fort Worth, aged 36, died October 1, of cerebral hemorrhage.

Dr. Charles Brooks Jones, Quanah, aged 52, died October 7, of angina pectoris.

Dr. George Cullen, Galveston, aged 62, died September 4, of angina pectoris

Dr. Jack Martin Estes, Abilene, aged 63, was killed October 10, when struck by an automobile.

Dr. F. A. Fuller, Jacksonville, aged 80, died October 11, of coronary occlusion, following a stroke of apoplexy.

Oxygen Says:

"During the past few years I have become an increasingly important factor to the Medical Profession. I am now being used pre-operatively, post-operatively, in pneumonia, asthma, chronic heart conditions, etc. BUT, to do my best work therapeutically, I must be administered immediately following diagnosis, and continued until I have completed my task."

"PURITAN MAID"
Cyclopropane
Nitrous Oxid
Ethylene
Oxygen
Carbon Dioxid
Percentage Mixtures of Carbon Dioxid and Oxygen

One of the most effective means for the administration of Oxygen in prolonged cases is the Nasal Catheter Method—used and recommended by Doctors who have made a study of the value of Oxygen therapy.

Our PURITAN NASAL CATHETER OUTFIT, as shown, is efficient, economical, portable, and durable.

Puritan Nasal Catheter Outfits
Leading Makes of Oxygen Tents
Bedside Inhalation Units
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Because we are interested at all times in placing quality products in the hands of our customers at the lowest cost possible, we are pleased indeed to remind you again of lower prices on "PURITAN MAID" CYCLOPROPANE—(produced by the improved process developed in the Chemical Research Laboratories of Purdue, and manufactured by MALLINCKRODT).

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All Types of Anesthetic Gas Machines
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NEW YORK BOSTON ST. PAUL DETROIT PHILADELPHIA

Dr. Edwin William Link, Palestine, aged 79, died October 24, of melanosarcoma.

Dr. Gregor Christopher McLeod, Lyons, aged 80, died October 6, of fracture of the hip and arteriosclerotic heart disease.

Dr. Charles W. Ory, Comanche, aged 64, died October 9, of cerebral hemorrhage.

Dr. John E. Reeves, Orange, aged 69, died September 20, of cerebral hemorrhage.

Dr. Charles Walker Skipper, Corpus Christi, aged 53, died October 17, of leukemia.

Dr. DeWitt Talmage Smith, Dallas, aged 49, died October 37, of heart disease.

Dr. Doras Lee Stephens, Anson, aged 72, died October 28, of heart disease.

Dr. Asa H. Speer, Corpus Christi, aged 61, died October 31, of acute malaria.

Dr. John Frank Taylor, Hamlin, aged 66, died October 18, of heart disease.

VIRGINIA

The Danville-Pittsylvania Academy of Medicine has elected the following officers: Dr. P. W. Miles, President, reelected; and Drs. L. O. Crumpler and E. E. Barksdale, Vice-Presidents, all of Danville.

Fredericksburg Medical Society has elected the following officers: Dr. Thomas W. Dew, President; Dr. J. M. Holloway, Vice-President; and Dr. Thomas B. Payne, Secretary-Treasurer, reelected, all of Fredericksburg.

The Lynchburg Academy of Medicine has elected the following officers: Dr. Elisha Barksdale, President; and Dr. S. E. Oglesby, Vice-President, both of Lynchburg.

The Richmond Academy of Medicine has elected the following officers: Dr. Austin I. Dodson, President; Drs. Charles M. Caravati and Ennion S. Williams, Vice-Presidents; and Dr. R. A. Nichols, Recording Secretary, all of Richmond.

The Southside Virginia Medical Association has elected the following officers: Dr. W. J. Ozlin, South Hill, President; Dr. Leta White, Petersburg, Dr. James A. Grizzard, Drewryville, Dr. John A. Proffitt, Burkeville, and Dr. J. Lewis Rawls, Suffolk, Vice-Presidents; and Dr. R. L. Raiford, Franklin, Secretary-Treasurer, reelected.

The Seaboard Medical Association of Virginia and North Carolina held its forty-second annual meeting at Virginia Beach, December 7-9, and elected the following officers: Dr. W. I. Wooten, Greenville, North Carolina, President; Dr. O. R. Yates, Suffolk, Dr. R. G. Tyndall, Kinston, North Carolina, Dr. C. P. Jones, Newport News, and Dr. G. B. Woodard, Wilson, North Carolina, Vice-Presidents; and Dr. Clarence Porter Jones, Newport News, Secretary-Treasurer, reelected. Greenville, North Carolina, was chosen as the place of the 1938 meeting, the dates being December 6-8.

The Medical College of Virginia recently announced that its new Outpatient Clinic had been completed. This eight-story building cost about $550,000, $300,000 of which was a gift of an anonymous donor and $239,850 a grant from the Public Works Administration.

The fourth graduate course in ophthalmology and otolaryngology was held at the University of Virginia Department of Medicine at the University Hospital December 14-17.

Dr. Joseph D. Collins, Portsmouth, was elected President of the Association of Seaboard Airline Railway Surgeons, held in Miami, Florida, in November, succeeding Dr. Beverley R. Tucker, Richmond.

Dr. Hugh C. Henry, Superintendent of the Central State Hospital at Petersburg, has been named Acting Superintendent of the Southwestern State Hospital at Marion.

Dr. Edward A. Delarue, Jr., Richmond, announces the opening of offices in the Medical Arts Building, for the practice of internal medicine.

Dr. Meyer Vitsky, Richmond, announces the limitation of his practice to obstetrics and gynecology.

Dr. Charles A. Bland, formerly of Clover, resigned from active duty as First Lieutenant, Medical Reserve Corps, U. S. Army, and is now engaged in general practice at Forest City, North Carolina.

Dr. William P. Frazer, Hamilton, was among those elected to the Board of Directors of the Loudoun County Junior Chamber of Commerce at its organization meeting recently.

Dr. E. R. Moorman, Kilmarnock, was named Vice-President, and Dr. Douglas G. Chapman, Richmond, Secretary of the Alumni Association of Roanoke College in Richmond area, organized early in December.

Continued on page 52

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SULISOCOL

TRADE MARK REG. U. S. PAT. OFF., PATENT NO. 1, 980, 236

for chronic arthritis

1. Improvement in focal symptoms, e.g., reduction of pain, swelling, stiffness, etc.

2. Improvement in constitutional symptoms, e.g., gain in weight, lessening of fatigue, increase in appetite, etc.

3. Reduction in the sedimentation rate and non-filament cell count.

Sulisocol is a valuable adjunct in the treatment of certain types of arthritis, especially those with low cystine content of the finger nails. Its use should not preclude the use of physiotherapy and hygienic measures as may be indicated in the judgment of the physician.

A course of treatment consists of 2cc (20 Mgm.) to 5cc (50 Mgm.) injected preferably intravenously twice or three times weekly for at least twenty-five injections beginning with 2cc.

HYPOSOLS

2cc 20 Mgm. boxes of 25, $ 8.50
3cc 30 Mgm. boxes of 25, $10.00
5cc 50 Mgm. boxes of 25, $12.50

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If direct, cash with order

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Long Island City, New York

Continued from page 50

Dr. William Roberts Tyson and Miss Elizabeth Gertrude Ehringhaus, both of Norfolk, were married, October 4.

Dr. Edward Carlisle Joyner, Suffolk, and Miss Ruth Elizabeth German, Richmond, were married December 6.

Dr. Snowden C. Hall, Danville, and Miss Ida Shankle Hardman, Commerce, Georgia, were married in December.

Deaths

Dr. William Jeffries Chewning, Fredericksburg, aged 60, died October 28, as a result of a stone impacted in the common bile duct.

Dr. Herbert Reney Drewry, Norfolk, aged 70, died December 1, after a long illness.

Dr. Thomas C. Harris, Centralia, aged 61, died December 6.

Dr. Robert Roy Hoskins, Mathews, aged 60, died December 20.

Dr. John F. Long, Luray, aged 88, died December 8.

Dr. Edward Massenberg Parker, Emporia, aged 72, died December 16.

Dr. C. Leonard Purdy, Broadnax, aged 69, died November 28.

Dr. Oliver Allison Ryder, Alexandria, aged 50, died November 27, following a heart attack.

WEST VIRGINIA

Central West Virginia Medical Society has elected the following officers: Dr. Everett Walker, Adrian, President; Dr. E. S. Brown, Summerville, Vice-President; and Dr. A. B. Bowyer, Buckhannon, Secretary-Treasurer.

Fayette County Medical Society has elected the following officers: Dr. F. S. Harkleroad, Harvey, President; Dr. Max Raine, Fayetteville, First Vice-President; Dr. A. E. Bays, Carbondale, Second Vice-President; and Dr. Gilbert Daniel, Alloy, Secretary-Treasurer.

Greenbrier Valley Medical Society has elected the following officers: Dr. H. D. Gunning, Ronceverte, President; Dr. Guy Hinsdale, White Sulphur Springs, Vice-President; and Dr. R. E. Baer, White Sulphur Springs, Secretary-Treasurer.

Harrison County Medical Society has elected the following officers: Dr. E. F. Wehner, President; Dr. O. W. Ladwig, Vice-President; Dr. George F. Evans, Treasurer; and Dr. James G. Ralston, Secretary, all of Clarksburg.

Kanawha County Medical Society has elected the following officers: Dr. B. H. Swint, Charleston, President; Dr. Martin L. Bonar, Charleston, Vice-President; and Dr. A. Spates Brady, Jr., Elkins, Secretary-Treasurer.

Lewis County Medical Society has elected the following officers: Dr. M. D. Cure, Weston, President; Dr. G. C. Corder, Jane Lew, Vice-President; and Dr. Robert O. Pletcher, Jane Lew, Secretary.

Logan County Medical Society has elected the following officers: Dr. D. T. Moore, Stirrat, President; Dr. J. W. Lyons, Holden, Vice-President; and Dr. J. L. Patterson, Holden, Secretary-Treasurer.

Marshall County Medical Society has elected the following officers: Dr. L. H. McKuskey, Moundsville, President; Dr. Homer A. Parker, McMechen, Vice-President; and Dr. J. A. Striebich, Moundsville, Secretary-Treasurer.

Mercer County Medical Society has elected the following officers: Dr. E. W. Horton, Bluefield, President; Dr. Gordon Todd, Princeton, Vice-President; Dr. O. G. King, Bluefield, Secretary; and Dr. H. G. Steele, Bluefield, Treasurer.

Parkersburg Academy of Medicine has elected the following officers: Dr. R. S. Widmeyer, President; Dr. E. T. Goff, Vice-President; and Dr. James L. Wade, Secretary-Treasurer, all of Parkersburg.

Wyoming County Medical Society has elected the following officers: Dr. Walter Dearing, Mullins, President; Dr. R. C. Hatfield, Oceana, Vice-President; and Dr. Ward Wylie, Mullens, Secretary-Treasurer.

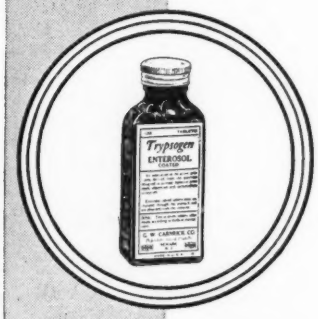
The Huntington Radium and X-Ray Clinic opened new quarters in the Memorial Hospital, Huntington, on November 11. Dr. James Edward Hubbard is Director, and Dr. Walter Beckett Martin is Associate Director of the clinic, which was founded in 1921.

Deaths

Dr. Traian Thomas Benchea, Wheeling, aged 39, died October 30, of bronchopneumonia.

Dr. D. C. Casto, Parkersburg, aged 60, died October 24.

Pancreas Therapy
BY
Oral Administration



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Effervescent

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Emerson's C-G Alkalizer is an effective agent for supplying alkali in those conditions in which there may be reduced alkali salts in the blood, in addition to supplying calcium where systemic calcium deficiencies exist. Uric alkalinity, running four to six hours, may be induced by one dose, repeated in a half hour. Six teaspoonfuls will furnish as much calcium as the average daily diet. Emerson's C-G Alkalizer does not upset the normal acid of the stomach, is not laxative, but does stimulate gastric function as well as promoting elimination through intestines, kidneys and skin.

Available in four and eight ounce bottles at a maximum prescription price of 75c and $1.25.

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EMERSON DRUG COMPANY, Baltimore, Md.
Please send me FREE a full-size market package of Emerson's C-G Alkalizer.

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*City*_____ *State*_____ SM 2

Infant Feeding Vessels of the STONE AGE

FEEDING vessels used for babies among aboriginal American tribes are rarely found. Those illustrated here, obtained from a famous museum collection, were excavated from mounds where only babies were interred.

Since these utensils were first employed, the style of infants' feeding bottles has undergone many variations. But even more revolutionary has been the change in the feedings. It has been said that more progress was made in this direction during the past three decades than in all the centuries preceding.

It may be more than a coincidence that during most of this period the one system of infant feeding that has gained outstandingly in pediatric acceptance is the use of the diluted cow's milk formula with Dextri-Maltose as the carbohydrate.

These infant feeding vessels, newly added to the group of ancient nursing bottles owned by Mead Johnson & Company, have been obtained from Edward W. Payne's internationally known collection of stone age relics.

Left to right, top row: Crude gray feeding bottle excavated from mound builders' grave in Missouri; rare teapot-shaped feeding vessel of red pottery, from Oklahoma mounds; unpainted feeding bottle from New Madrid, Missouri.

Center row: Unglazed pottery bottle showing crude thumb-prints of the maker, from Ogdensburg, Missouri; red glazed pottery bowl from Arkansas; decorated reddish brown bottle with slight glaze, from Neutrozo Creek, Arizona.

Bottom row: Papoose spoon similar to pap boat, from Hovenweep Canyon, Colorado; tiny feeding cup (capacity only 3 tablespoons), from Arizona; gray pottery feeding bottle with brown design, also from Arizona.

When requesting samples of Dextri-Maltose, Pablum, and other Mead products, please enclose professional card to cooperate in preventing their reaching unauthorized persons. Mead Johnson & Company, Evansville, Indiana, U. S. A.

It Can Happen Here

Example of severe rickets in a sunny clime. Courtesy of E. H. Christopherson, M.D., San Diego, and of "California and Western Medicine."

LEST WE FORGET—we who are of the vitamin D era—severe rickets is not yet eradicated, and moderate and mild rickets are still prevalent. Here is a white child, supposedly well fed, if judged by weight alone, a farm child apparently living out of doors a good deal. This boy was reared in a state having a latitude between 37° and 42°, where the average amount of fall and winter sunshine is *equal to that in the major portion of the United States*. And yet such stigmata of rickets as *genu varum* and the quadratic head are plain evidence that rickets does occur under these conditions.

How much more likely, then, that rickets will develop among city-bred children who live under a smokepall for a large part of each year. True, vitamin D is more or less routinely prescribed nowadays for infants. But is the antiricketic routinely administered in the home? Does the child refuse it? Is it given in some unstandardized form, purchased from a false sense of economy because the physician did not specify the kind?

A uniformly potent source of vitamin D such as Oleum Percomorphum, administered regularly in proper dosage, can do more than protect against the gross visible deformities of rickets. It may prevent hidden but nonetheless serious malformations of the chest and the pelvis and will aid in promoting good dentition. Because the dosage is measured in *drops*, Oleum Percomorphum is well taken and well tolerated by infants and growing children. Rigid bioassays assure a uniform potency—100 times the vitamins A and D content of cod liver oil*. Oleum Percomorphum, moreover, is a natural product in which the vitamins are in the same ratio as in cod liver oil*.

*U.S.P. Minimum Standard

Oleum Percomorphum offers not less than 60,000 vitamin A units and 8,500 vitamin D units (U. S.P.) per gram. Supplied in 10 and 50 c. c. brown bottles, also in 10-drop soluble gelatin capsules, each offering not less than 13,300 vitamin A units and 1,850 vitamin D units, in boxes of 25 and 100.

MEAD JOHNSON & COMPANY, EVANSVILLE, INDIANA, U.S.A.

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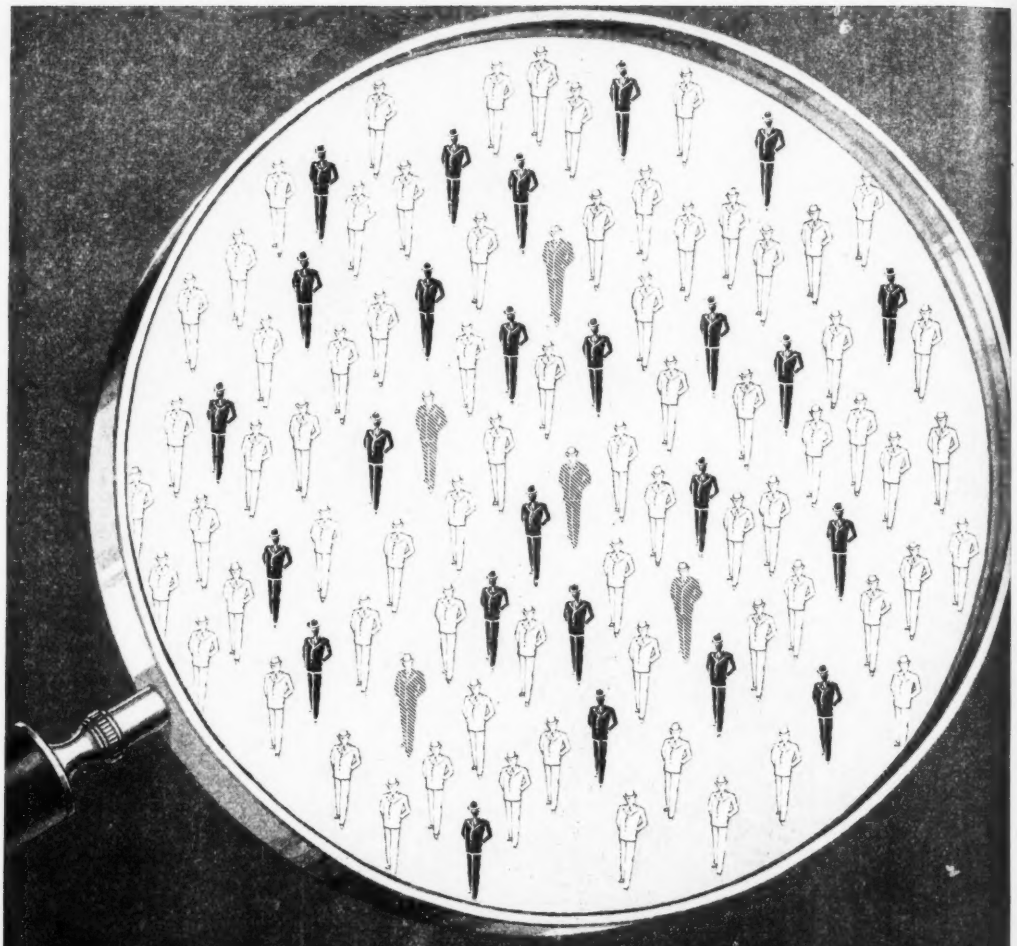

Those 25 Patients who can be saved

Of one hundred cases developing type I pneumonia, seventy will recover and five will die regardless of treatment. The remaining twenty-five will die without treatment, but can be saved by prompt administration of Antipneumococcic Serum, Felton.

Reports in recent medical literature have shown that the very early use of specific antipneumococcic serum is important. In a series of 160 type I pneumonia cases (R. L. Cecil J. A. M. A. 108:689, 1937) in which specific antiserum was given within twenty-four hours of onset, mortality was reduced to one-third the usual rate in serum-treated cases, and to one sixth the average rate in cases not receiving serum.

Antipneumococcic Serum (Felton) Type I, Refined and Concentrated, is available in syringe packages containing 10,000 and 20,000 units; Antipneumococcic Serum (Felton) Types I and II, Refined and Concentrated, in syringe packages containing, respectively, 10,000 and 20,000 units of each type.

PARKE, DAVIS & COMPANY · *Detroit, Mich.*

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